The Neurobiology of Social Cognition: Role of the Posterior Cingulate Cortex

by

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Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor
of Philosophy in the Department of
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ABSTRACT

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Abstract

It has been suggested that primate brains are inherently biased towards gathering and processing the social information present in the world. In fact, the neural network that mediates our engagement with the external world – the default mode network (DMN) – is strongly convergent with the neural circuitry for social cognition. The posterior cingulate (PCC) is believed to be a key node in both the DMN and in social cognition. Human and non-human primate studies have demonstrated a role for the PCC in outcome monitoring: it tracks rewards, subjective values of choices, task engagement and global choice strategies. It is also implicated in social cognition. Human studies show that PCC activity varies with the recall of autobiographical memories and exposure to social stimuli. While several electrophysiological studies explicate the response of PCC neurons to non-social outcome monitoring and valuation, there is a lack of similar studies for social valuation. This thesis is concerned with characterizing the neuronal responses in the PCC to social stimuli and determining whether social valuation occurs in the PCC in a manner similar to that previously described for non-social outcomes. I recorded the single unit activity of neurons in the PCC of rhesus macaques while they performed behavioral tasks that required attending to the faces of high-status or low-status individuals. Monkeys valued the faces of high-status individuals more than low-status individuals, though they were equally likely to

identity and overtly attend to faces of both social classes. This differential valuation of face stimuli was represented in the firing activity of PCC neurons, with higher neuronal activity seen in response to subordinate faces as compared to dominant ones. Cells in the PCC did not track the individual identity of the presented faces. Furthermore, neuronal activity in the PCC predominantly tracked social value, and not non-social reward delivery as previously reported. Neuronal activity also predicted task engagement, with higher firing rates being predictive of a decrease in task engagement. To summarize, the PCC is biased towards social information processing, and neuronal activity in the PCC tracks the salience of social information.

Dedication

To Wodehouse,

for keeping me laughing all these long years.

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List of Abbreviations

ACC Anterior cingulate cortex

DA Dopamine

DMN Default mode network

dmPFC Dorsomedial prefrontal cortex

FFA Fusiform face area

GABA gamma-Aminobutyric acid

LIP Lateral intraparietal area

lPFC Lateral prefrontal cortex

MTL Medial temporal lobe

NMDA N-methyl D-aspartate

OFC Orbitofrontal cortex

PCC Posterior cingulate cortex

SNc Substantia niagra pars compacta

STS Superior temporal sulcus

vmPFC Ventromedial prefrontal cortex

VTA Ventral tegmental area

Acknowledgements

Before joining the lab, my exposure to non-human primates was restricted to watching episodes of Curious George and my computer skills were limited to updating my Facebook status. If I have accomplished anything since, it is because of the unflagging support of my advisors, colleagues, friends, and family. I would like to acknowledge the tremendous help the Platt lab has extended me: Dr. Michael Platt, who has been more patient with me than was strictly warranted; Ben, Karli, John, and Steve, who taught me everything I know about primate training and electrophysiology; and Kara Moore and Monica Carlson, for taking care of our monkeys (and us). I would also like to thank my thesis committee members – Richard Mooney, R. Alison Adcock, and Elizabeth Brannon – for providing me with advice and encouragement. And finally, Solly, without whom this thesis would be impossible.

1. Introduction

Scientists in popular culture are often depicted as the unkempt, badly dressed, but brilliant "absent-minded professors", so engrossed in work that they often forget about their surroundings. There are, of course, numerous examples of scientists living up to this trope, from Thales, the 6th century Greek philosopher who was so focused on observing the skies that he fell down a well, to modern-day mathematician, Norbert Wiener, who not only forgot the location of his house but also his daughter. As the "absent-minded professor" demonstrates, we constantly struggle to balance our internal and external worlds: to focus on our internal goals and pursuits, or to explore and navigate the external world.

Our daily lives are governed by a constant need to shift attention between a series of conflicting goals and stimuli. We are required to adjust our engagement with the world; balancing our stimulus-independent internal goals against our stimulus-dependent behavior. Norbert Weiner, for example, was focused on his internal goals (explicating mathematical concepts) to the detriment of correctly responding to external stimuli (failing to recognize his daughter). Thus, we are required to constantly redeploy our attention between monitoring our internal milieu and the external environment.

Despite the importance of balancing our internal goals and external stimuli, the neural substrates that underlie this redistribution of network load are not well

understood. The posterior cingulate cortex (PCC) has been strongly implicated as one of the key nodes in the neural system that helps balance our internal goals and external stimuli. This thesis focuses on the possible role of the PCC as a mediator of balancing our internally-driven and externally-driven information processing.

1.1 The posterior cingulate cortex: introduction

The posterior cingulate cortex is one of the most metabolically demanding regions of the mammalian cortex, consuming more glucose than any other cortical region in humans (Harley and Bielajew 1992). PCC dysfunction is associated with several clinical disorders, including schizophrenia and Alzheimer's disease (Garrity et al 2007, Hirono et al 1998, Huang et al 2002, Mitelman et al 2005). The PCC has also been implicated in a number of seemingly disparate functions, including sensory and motor signaling (Olson et al, 1996, Olson and Muscil 1992, Vogt 1992), spatial learning, navigation and orienting (Gron et al 2000, Hirono et al 1998, Sutherland et al 1998), evaluation of and tracking outcomes (Hayden et al 2008, McCoy et al 2003, McCoy and Platt 2005, Vogt et al 1992), mind wandering (Mason et al 2007), autobiographical memory retrieval (Maddock et al 2001, Svoboda et al 2006) and processing emotionally-salient stimuli (Maddock et al 2003). However, despite the apparent importance of the PCC, there is still no unifying theory as to its function.

Across the literature the PCC is involved in three distinct and seemingly

disparate domains: the default mode network, social cognition, and reward or outcome monitoring and evaluation. In this introduction, I shall discuss the PCC and its role in each of these areas.

1.2 The anatomy of posterior cingulate cortex

The cingulate cortex is situated in the medial aspect of the cerebral cortex (Figure 1A). Its name is derived from the Latin word for belt (cingulum), indicating its position as the cortical region that encircles the corpus callosum. Cytoarchitecturally, it has been divided into several distinct Broadmann areas: 23, 24, 25, 26, 29, 30, 31, 32, and 33. The more rostral of these have been grouped as the anterior cingulate cortex (ACC): 24, 25, 32 and 33, while the more caudal is the posterior cingulate cortex (PCC) consisting of Broadmann areas 23, 29, 30, and 31. The main anatomical distinction between the ACC and the PCC appears to be the cortical layer 4, which is thin and agranular in the ACC but thicker and granular in the PCC. These anatomically separate regions within the cingulate cortex seem to serve distinct functional roles. The PCC can be further sub-divided into at least two distinct regions: the rostral PCC (Broadmann areas 23 and 31) and the more caudal retrosplenial cortex (Broadmann areas 29 and 30). Interestingly, the retrosplenial cortex constitutes the entirety of the PCC homolog in rodents (Yukie et al 2009). Conversely, the retrosplenial cortex is reduced to a mere sliver in primates, with Broadmann areas 23 and 31 dominating the territory occupied by the PCC. It is as yet unknown whether the rodent retrosplenial cortex serves a similar function to the

primate PCC. This makes non-human primates a more appealing animal model for understanding the function of the human PCC (For review see Hayden and Platt 2009).

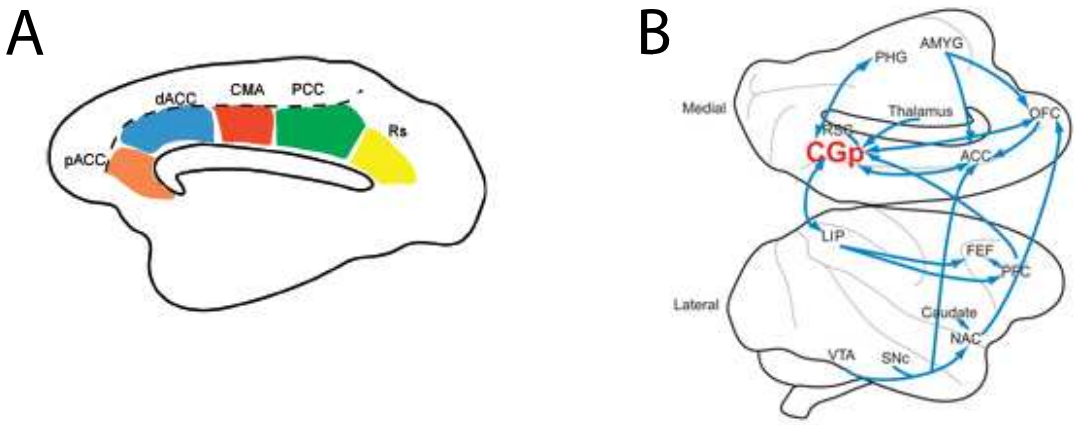

Figure 1: Location (A) and notable neuroanatomical connections (B) of the PCC. Taken from (Hayden and Platt 2009, Pearson et al 2011)

The PCC is a highly interconnected region of the cortex, both receiving and sending projections from other cortical regions and the limbic system (Vogt et al 1992). Some of the notable connections of the PCC include projections to the lateral prefrontal cortex (lPFC), orbotifrontal cortex (OFC), ACC, and the medial temporal lobe (MTL) (Figure 1B). The connections of the PCC argue for its role in orienting attention, learning and memory, social cognition, and in the emotional aspects of cognition.

The PCC shares massive reciprocal connectivity with the ACC. The ACC has been implicated in outcome evaluation and action selection (Rushworth and Brehens 2008). Additionally, the ACC responds strongly to error outcomes, with an increase in activity related to the magnitude of the possible reward (Amiez et al 2005). Similar error-

related signals have also been described in the PCC (McCoy et al 2003), arguing for a role for the cingulate cortex in outcome evaluation.

The PCC also has strong reciprocal connections with structures of the MTL, notably the perirhinal cortex, entorhinal cortex and the parahippocampal gyrus (Vogt et al 1992, Vogt et al 1979, Yukie and Shibata 2009). The MTL is known to be critical for learning and memory (Squire et al 2004), arguing for a complementary role for the PCC. Indeed, firing of neurons in the PCC is believed to reflect the regulation of active learning (Heilbronner 2012). The MTL is also required for the formation of declarative long-term memory, which includes episodic or autobiographical memories (Smith 2007). Given the connectivity between the PCC and the MTL, a role for the PCC in autobiographical memory processes could be posited. Indeed, the PCC is believed to be involved in the retrieval of autobiographical memories. fMRI studies reveal PCC activation while individuals recall autobiographical memories (Fink et al 1996, Maddock et al 2001). Furthermore, lesions and dysregulation of the PCC lead to deficits in the process of autobiographical memory retrieval (Minoshima et al 1997, Valenstein et al 1987).

The PCC is also connected to the OFC, both anatomically and functionally. The OFC is involved in emotional and motivational information processing (Schoenbaum et al 2011). The OFC appears to play an important role in social cognition, and social

stimulus appears to have privileged access to it (Watson and Platt 2012). Damage to the OFC renders individuals unable to identity facial expression (Hornack et al 1996, Hornack et al 2003), and display poor social judgments (Eslinger and Damasio 1985, Willis et al 2010) and behavior (Beer et al 2006, Cicerone and Tanenbaum 1997). Given the reciprocal connections that exist between the PCC and the OFC, there seems to be a strong argument for the PCC in social cognition.

1.3 Default mode network

The default mode network (DMN) of the brain is a set of cortical regions that are "activated" during rest and "deactivated" during performance of a cognitively challenging task. The DMN is characterized by high metabolic and hemodynamic activity during rest (Buckner et al 2008), and a suppression of this activity during goal-directed tasks. Activation of the default network is typically anti-correlated with activation of brain regions implicated in selective attention.

The discovery of the DMN was serendipitous. Early imaging studies were designed to observe brain activity while subjects were engaged in cognitively challenging tasks, and the control state used for comparison was the "rest" state. Initial hypotheses posited that there would be an increase in brain metabolic activity when subjects were involved in active task participation, but results did not bear this out. Instead, vigorous and persistent brain activity was observed even in the rest state. David Ingvar first aggregated these initial studies and noted the presence of consistent and

regionally-specific brain activity in the rest state (Ingvar 1974, 1979, 1985), and suggested that this corresponded to "undirected, spontaneous, conscious mentation, the brain work which we carry out when left alone undisturbed" (Ingvar 1974). Subsequent studies and advances in imaging techniques refined this initial finding. Notably, Raichle, Gusnard and colleagues compiled a significant array of data to study baseline brain activity, which they termed "default mode", and discover the cortical regions subserving it.

1.3.1 Anatomy of the DMN

The collective set of brain structures that comprise the DMN can be reliably identified in resting state fMRI studies. The core regions associated with the DMN include the ventral medial prefrontal cortex (vmPFC), the PCC, the lateral temporal cortex (LTC), the dorso medial prefrontal cortex (dmPFC) and the hippocampal formation (Buckner et al 2008, Raichle et al 2001). The involvement of these regions has been based primarily on task-induced deactivations observed in these regions and on functional connectivity analysis. The integrity of the DMN seems to be compromised in several neurological disorders, including Alzheimer's Disease (Sorg et al 2007, Hafkemeijer et al 2012), schizophrenia (Garrity et al 2007, Zhou et al 2007), and autism (Kennedy et al 2006).

Interestingly, the idea that the DMN is characterized by high activity only during non-task related "rest" periods has been called in to question (Kelly et al 2012,

Murphy et al 2009). In fact, the brain regions implicated in the DMN are strongly activated in tasks involving social cognition, and there exists a remarkable overlap in the brain regions implicated in the DMN and those implicated in social cognition (Corbetta et al 2008, Mars et al 2012, Schilbach et al 2008).

1.3.2 Potential role of the DMN

The DMN is characterized by high activity during rest periods and a task-related deactivation. The DMN has been implicated in numerous diverse processes, and its function remains highly debated. It has been implicated in memory processes including memory encoding (Daselaar et al 2004) and retrieval (Maddock et al 2001), emotion (Maddock et al 2003), temporal projection of the self (Buckner and Carroll 2007, Spreng and Grady 2010), decision-making (Kable and Glimcher 2007), mind-wandering (Mason et al 2007), and monitoring the environment (Gilbert et al 2006, Gilbert et al 2007, Ghatan et al 1995). Generally, these divergent studies have been integrated such that two main hypotheses to explain the function of the DMN have been proposed.

1.3.2.1 Monitoring the external environment

Deactivation of the DMN has been implicated in attention and task engagement. The "sentinel" hypothesis posits that the DMN monitors the external environment (Ghatan et al 1995, Shulman et al 1997, Gusnard and Raichle 2001, Hahn et al 2007). Monitoring the external environment, and any change observed therein, is critical for decision-making and behavior. Active task participation suppresses this broad

monitoring of the environment, instead requiring focused attention on presented stimuli and cues. The suppression of the DMN during active task engagement suggests a role for the DMN in information gathering as opposed to actively attending to the task. Thus, in this scheme of either task-related or exogenous (environmental monitoring) attention, the DMN participates in collecting exogenously driven information gathering; it mediates task disengagement and promotes exteroceptive vigilance (Hahn et al 2007).

In keeping with this hypothesis, activity within the DMN is associated with lapses in attention (Weissman et al 2006) and lack of task engagement (Daselaar et al 2004). The DMN also shows a strong deactivation in individuals participating in a cognitive task, and the degree of deactivation is strongly predictive of performance on the task (Eichele et al 2008). This has been further substantiated by neuronal activity recorded in the PCC of macaques performing simple attentive and memory tasks (Hayden et al 2009). Firing rates of PCC neurons were reliably suppressed while subjects were actively engaged, and higher firing rates predicted errors and slower behavioural responses. It appears that the DMN signals the subject's level of task engagement, with higher activity in the DMN indicating a lack of task engagement.

1.3.2.2 Internal Mentation

An alternative hypothesis regarding the role of the DMN is that of "internal mentation". Internal mentation is the self-reflective thoughts and judgments that depend

on stimulus-free social, emotional and intellectual content (Gusnard et al 2001, Mitchell et al 2006).

The possible role of the DMN in internal mentation is informed by our understanding of the "rest" state. It has been suggested that the rest state could be more accurately called the R.E.S.T. state: an acronym for "random episodic silent thinking" (Andreasen et al 1995). An early study that advanced the idea of the DMN in internal mentation (Andreasen et al 1995) showed that the same brain regions active during the rest state were also recruited when the subject was required to actively perform a task requiring the recall of past autobiographical memory. A number of subsequent studies have shown that tasks that recruit the processes underlying internal mentation – autobiographical memory, envisioning the future, mentalizing – all show consistent and strong activation of the DMN (Andreasen et al 1995, Fletcher et al 1995, Maguire 2001, Maddock 2001, Maddock 2003, Rilling et al 2004, Saxe et al 2004). Thus, the activation observed within the DMN during the rest state is a reflection of the internal mentation of subject who has been released from cognitively challenging task demands.

1.3.3 The PCC and the DMN

The single most consistently and dramatically modulated brain region within the DMN is the PCC (for review see Buckner et al 2008). The PCC has the highest levels of metabolic and hemodynamic activity of any of the cortical regions, including those

implicated in the DMN (Harley and Bielajew 1992). Additionally, the PCC also shows strong reciprocal connections with other structures of the DMN (for review see Buckner et al 2008). It has been proposed that the PCC is a critical structure within the DMN, possibly serving as a central hub for the DMN. In fact, imaging studies attempting to identify the DMN within individual subjects using functional connectivity most often place the seed region of their analysis in the PCC (Buckner et al 2008, Fox et al 2005, Grecious et al 2003, Grecious et al 2004).

Interestingly, stimuli and tasks parameters that modulate activity within the PCC support both proposed roles of DMN function. The sentinel hypothesis of DMN function proposes that the DMN is involved in maintaining the balance between task-related and broad environmental information processing, and that deactivations within the DMN indicate enhanced active task participation and engagement. Indeed, neuronal activity within the PCC is suppressed preceding active task participation, and increased activity is predictive of a lack of task engagement (Hayden et al 2009). Furthermore, differential recruitment of the DMN is also seen in a task that requires subjects to switch between exploitative and exploratory (global monitoring of environment) strategies, with activation in the DMN predicting a switch between these two global strategies (Daw et al 2006, Pearson et al 2009).

Persistent activity within the PCC appears to signal the need to switch between

alternative strategies. In a simple risk-choice task, firing activity within the primate PCC is strongly predictive of a change in choice strategy (Hayden et al 2008). In a more complex dynamic foraging task that requires subjects to maximize reward output by choosing between an exploitative or exploratory strategy, activity of primate PCC neurons signals, in a graded fashion, impending changes in strategy (Pearson et al 2009). Furthermore, microstimulation within the primate PCC results in subjects switching strategy and choosing a non-preferred option over the standard preferred one (Hayden et al 2008). Thus, activity within the PCC precedes and predicts a change in behavioural strategy. Finally, bilateral lesions of the PCC can cause Balint's Syndrome (Mesulam 2000), which is characterized by patients being able to attend to objects only within a limited focus of attention. Objects external to this narrow tunnel of attention often remain undetected (Mesulam 2000). This disruption in exteroceptive vigilance is what we would expect if the PCC were involved in a system that mediates global attention. Collectively, this suggests that the PCC, in keeping with the sentinel theory, is involved in the redeployment of attention between task-focused and exteroceptive vigilance. Suppressed activity within the PCC favors task engagement, while increased PCC activity favors a change of state to promote a more flexible exploratory environment.

The alternative theory for DMN function suggests that it drives the cognitive processes underlying internal mentation: including, referential and autobiographical memory recall, mind wandering, mentalizing and ascribing theory of mind to others,

and cognitive housekeeping. These varied processes – memory recall, mentalizing and ascribing thoughts and intentions to others, envisioning the future – are thought to be bound together by the need to construct mental simulations (Buckner and Carroll 2007). Not surprisingly, tasks designed to probe these varied aspects of cognition result in the robust recruitment of the PCC. PCC activation is seen in tasks that require subjects to recall autobiographical memories (Andreasen et al 1995, Daselaar et al 2004, Maddock et al 2001). A meta-analysis of PET and fMRI studies of autobiographical memories highlights the consistent involvement of the PCC in autobiographical memory retrieval (Svoboda et al 2006). Studies of the theory of mind also reliably result in activation within the PCC (Rilling et al 2004, Saxe et al 2004, Saxe and Powell 2006). Additionally tasks that require envisioning the future also reliable activate the PCC (Schacter et al 2007, Schacter et al 2008). Mind wandering has also been shown to result in PCC activation (Mason et al, 2007). Thus, there is robust activation within the PCC in tasks that recapitulate the processes of internal mentation.

1.4 The social brain

Social interactions are essential components in an animal's behavioral repertoire, with the face serving as one of the most important stimuli underpinning social interactions (Altman 1967). In primates, recognition of faces serves as an accessible and reliable means of individual identification (Parr and de Waal 1999, Parr 2003). However, the recognition of faces is a complex phenomenon, involving not only processing the

identity of the face presented but also extracting related salient information (for example, facial expression or gaze direction). Evidence from psychiatric disorders points to the existence of two distinct neural circuits for face recognition (Ellis and Young 1990): one involved primarily in overt recognition of invariant features of the face ('person identity') and the second in recognition of the variant and affective features associated with a face (for example, the expression, gaze direction, familiarity, and autobiographical memories associated with the face). It has been suggested that the PCC and the superior temporal sulcus (STS) are key regions in the pathway for affective processing of social information (Ellis and Young 1990, Ellis and Lewis 2001). Imaging studies suggest that these regions are activated in response to affective information present in faces, including expressions (Critchley et al 2000, Hasselmo et al 1989, Narumoto et al 2001) and eye-gaze direction (Hasselmo et al 1989, Perrett et al, 1985) for the STS, and autobiographical relevance (Maddock et al 1999, Maddock et al 2001) and emotional salience (Lane et al 1997, Phillips et al 1997) for the PCC.

There exists a large body of literature, primarily in humans, linking the PCC to social cognition and social stimuli. An interesting insight into the role of the PCC in social cognition comes from a subtle and bizarre disorder, Capgras' Delusion, that occurs following lesions to cortical regions including the PCC (Ellis and Young 1990, Breen et al 2000). This delusional misidentification disorder results in the generation of "doubles" wherein the affected individual can overtly recognize a familiar face, but

attributes it as belonging to an imposter or double (Ellis and Lewis 2001, Berson 1983). Furthermore, the value associated with familiar faces, as indexed by changes in skin conductance responses, is lost in Capgras' Delusion (Ellis and Lewis 2001, Perrett et al 1992, Wicker et al 1998). Thus, it appears that damage to the PCC and surrounding cortical regions results in the specific loss of affective salience associated with familiar faces.

Indeed, activation in the PCC is often coupled with emotionally-salient social stimuli (Lane et al 1997, Phillips et al 1997), imaging studies showing increased activation within the PCC to emotionally-charged faces (Phillips et al 1997) and familiar faces (Leveroni et al 2000, Phillips et al 1998, Shah et al 2000). Additionally, there seems to be a close correlation between activity in the PCC and stimuli involving autobiographical memory, such stimuli being emotionally salient (Maddock et al 2001). Hypometabolism within the posterior cingulate is often predictive of early Alzheimer's disease – which involves loss of autobiographical memory and a corresponding decrease in autonomic recognition of familiar faces (Minoshima et al 1997, Reiman et al 1996).

Taken together, there is good reason to believe that the PCC is involved in social cognition, possibly by processing affective information associated with social (particularly face) stimuli.

1.5 Outcome evaluation

There is a growing body of literature on the role of the PCC in non-human primates, largely single unit recordings within the macaque PCC. The work focuses primarily on the role of the PCC in decision-making. An important aspect of decision-making is outcome evaluation, namely monitoring the outcome of a decision in order to better inform future decisions. Individuals compare the observed outcome to the expected outcome, evaluate the advantageousness of the outcome, and then modify future behavior if required. Vogt and colleagues (Vogt et al 1992) have suggested that the PCC is involved in this outcome evaluation.

An evaluative function for the PCC is consistent with various electrophysiological data. Neurons within the PCC respond to fluid rewards (McCoy et al 2003), Studies looking at BOLD signals and single-unit activity in the PCC suggest that it also tracks the subjective value of a reward (Kable and Glimcher 2007, Levy et al 2001, McCoy and Platt 2005). Furthermore, PCC neurons also respond following omission of predicted rewards and larger than expected rewards (McCoy et al 2003), encoding a reward prediction error.

Activity within the PCC however does not seem to be restricted to monitoring reward outcomes. Firing activity within the PCC also seems to precede changes in behavioural strategy in both a simply choice task (Hayden et al 2008) and in a complex

dynamic foraging (Pearson et al 2009). A causal role for the PCC in strategy switching has also been demonstrated with microstimulation disruptions of PCC function. Microstimulation within the PCC results in subjects switching strategy and choosing a non-preferred option over the standard preferred one (Hayden et al 2008). Thus, activity within the PCC precedes and predicts a change in behavioural strategy. The PCC not only appears to track task-relevant variables (including reward value), but to also use that information to implement future changes in behavioural strategy.

1.6 Pathologies of the PCC

Neuroanatomist James Papez suggested that the PCC was a critical component of 'Papez's Circuit', a neuroanatomical pathway involved in emotional processing in mammals (Papez 1937). This hypothesis led to the use of bilateral cingulotomies, as an alternative to the standard prefrontal lobotomy, to alleviate symptoms of chronic depression, schizophrenia, and obsessive-compulsive disorder (Corkin 1980). While this surgical intervention did occasionally alleviate the symptoms of the disorder being treated, it also resulted in a blunting of emotions (Dougherty et al 2002).

Lesions of the PCC usually occur in conjunction with lesions of the adjacent cortical regions, including the ACC and the retrosplenial cortex. Lesions of the cingulate cortex result in deficits in spatial learning and memory (Katayama et al 1999, Murray et al 1989), and in learning and recalling task rules (Burgess et al 2000). When cingulate

lesions occur in conjunction with those in MTL, both retrograde and anterograde amnesia can occur (Valenstein et al 1987). Lesions encompassing the PCC can also cause more subtle disruptions to autobiographical recall and valuation of social stimuli, leading to Capgras' Disorder (Breene et al 2000, Ellis and Young 1990).

There is another well-known pathology associated with dysfunction of the PCC: Alzheimer's Disease, a neurodegenerative disorder affecting more than 12 million people worldwide (Citron 2004). It is the most common form of dementia, accounting for an estimated 60 – 80 % of all cases of dementia, and is most commonly diagnosed in individuals over the age of 65 (Brookmeyer et al 1998). Alzheimer's Disease is characterized by a gradual deterioration in neurological function, progressing from an initial apathy, depression, and short-term memory loss to impaired judgment, disorientation and long-term memory loss.

While the root cause of Alzheimer's Disease remains largely unknown, the PCC has been strongly implicated in disease progression and prognosis. Within the brain regions affected in Alzheimer's Disease, the largest and earliest hyporegulation is observed within the PCC (Minoshima et al 1997). Additionally, the PCC hypometabolism precedes and strongly predicts the severity of disease progression (Huang et al 2002, Valla et al 2001). PCC metabolic abnormalities correlate with the severity of several symptoms of Alzheimer's Disease, including loss of autobiographical

memory (Minoshima et al 1997), learning deficits (Hirono et al 1998), and cognitive decline (Yoshiura et al 2002). In fact, this hypometabolism is so consistently observed in patients that it is used as a diagnostic tool for Alzheimer's Disease (Bonte et al 2004).

1.7 Hypothesis and aims

Electrophysiological studies using animal models (rhesus macaques) have greatly informed our understanding of the PCC. Such studies of the PCC have implicated the PCC in numerous diverse functions, including signaling the subjective value of chosen options (McCoy and Platt 2005), omission of reward (McCoy et al 2003), strategy switching (Hayden et al 2008, Pearson et al 2010), and task engagement (Hayden et al 2009). However, there has been a dearth of studies looking at the response of neurons in the PCC to social stimuli. It is important to address this lack of neurophysiological understanding of the PCC given that human imaging studies have strongly implicated the PCC in social cognition.

Primate (particularly human) intelligence is believed to be biased towards processing social information (Mesoudi et al 2006). A reasonable deduction would be that the physiological baseline of the brain is also the psychological baseline, i.e. the default mode of the brain is social cognition. In fact, a growing number of studies have suggested that the default mode of the brain is social (Schilbach et al 2008, Mars et al 2012), though the evidence is restricted to functional neuroimaging data from humans.

Neurophysiological studies, particularly single unit recordings and perturbations of the PCC, will be vital to furthering our understanding of the PCC, DMN and their relationship to social cognition.

Human imaging studies have shown that the PCC responds to emotionally-salient social stimuli, notably to emotionally-charged faces (Phillips et al 1997) and to familiar faces (Leveroni et al 2000, Phillips et al 1998, Shah et al 2000). Furthermore, a face recognition disorder involving the PCC – Capgras' Syndrome – involves the loss of the affective recognition of faces. It has been previously suggested (Ellis and Young, 2001) that the PCC is critical for the affective recognition of faces, as opposed to explicit or overt recognition. Thus, a role for the PCC in affective valuation of faces has been hypothesized, as opposed to individual identity recognition. This is further borne out by electrophysiological studies in macaques that have shown that the neuronal activity in the PCC tracks the subjective value of juice rewards (McCoy and Platt 2005). Thus, it would be illuminating to study neuronal activity of PCC in response to social stimuli to determine whether cells track the subjective value of social images in a manner similar to fluid rewards.

An interesting parallel to be drawn here is with the study of the OFC. There is a substantial body of work demonstrating that the OFC responds to the value of gustatory, fluid reward outcomes (Padoa-Schioppa and Assad 2006, Rolls et al 1989,

Tremblay and Schultz 1999, Wallis and Miller 2003). However, when monkeys are provided with both a social stimulus in addition to a juice reward, the majority of task-responsive cells track image category as opposed to fluid reward (Watson and Platt 2012). It appears that the social information has privileged access to the OFC, with cells in the OFC signaling the value of social images. Given the reciprocal connectivity between the OFC and the PCC, this begs the question whether social information has privileged access to the PCC in a manner similar to that seen in the OFC.

We can make several predictions about the function of the PCC in social cognition, based on what we know of the role of the PCC in subjective value and fluid reward monitoring, the DMN, and social cognition:

1) The PCC should respond to the subjective value of social stimuli. The PCC tracks the subjective value of choices that yield fluid rewards (Kable and Glimcher 2007, Levy et al 2011, McCoy and Platt 2005). Furthermore, studies of human patients and imaging studies have implicated the PCC in tracking the subjective value of social images (Ellis and Young 1990, Ellis and Lewis 2001). Thus, we hypothesize that the PCC tracks the subjective value contained in social images, with neuronal activity in the PCC firing differentially based on the value the organism places on the social stimulus.

2) The PCC responds to affective value information contained in social stimuli, as opposed to explicit identity. Human data, encompassing imaging studies and the

study of patients with deficits in face recognition, suggest the existence of two distinct pathways underlying the recognition of faces: one concerned with individual identity and the overt recognition of faces, and the second pathway for extracting the relevant affective information contained in faces, including their subjective value (Ellis and Young 2001, Ellis and Lewis 2001). Human imaging studies have shown that the PCC responds to emotionally-salient face images (Leveroni et al 2000, Phillips et al 1998, Shah et al 2000) and it has been suggested that the PCC has a role in tracking the affective information contained in faces, as opposed to the identity of the face. Thus, we can hypothesize that this will be reflected at the level of single unit recordings, where cells track the value of a face as opposed to its explicit identity.

3) The PCC has a role in task engagement. One of the most common roles ascribed to the PCC and the DMN is in task-engagement. Deactivations in the PCC commonly precede task engagement (Buckner et al 2008, Hayden et al 2009), and furthermore increased activity in the PCC is predictive of a lack of task engagement as indexed by errors and slower reaction times (Eichele et al 2008, Hayden et al 2009). It has been suggested that the task-related deactivations seen in the PCC are distinct from the responses seen to fluid rewards. Thus, we can predict that neurons in the PCC will manifest both a task-induced deactivation in addition to signaling the value of social stimuli.

These predictions yield two specific aims:

Aim 1: To determine whether neurons in the PCC signal the subjective value contained in social stimuli

It has been previously reported that monkeys value social images belonging to different social categories differently (Deaner et al 2003, Klein et al 2005, Watson and Platt 2012), such that they are willing to sacrifice fluid reward to view the faces of dominant monkeys and require larger than normal fluid reward in order to choose to view the faces of subordinate monkeys. I recorded neuronal activity within the PCC in a task in which subjects' choices are biased by the subjective value of monkey faces. Data suggest that neurons track the subjective value of faces, and seemingly do so in preference to information regarding fluid reward.

Aim 2: To determine whether neurons in the PCC signal the individual identity of faces

While the first task probed the subjective value of social stimuli, our second task required monkeys to correctly identity individual conspecifics. Data indicate that neurons track the subjective value of faces, namely their social category, and not individual identity of faces. Notably, this tracking of social value is seen in a task where the social category of the face is irrelevant to successful completion of a trial. Furthermore, neurons do not track the outcome of a trial.

The data show that the PCC responds preferentially to social stimuli as opposed

to fluid rewards when both are present. Furthermore, the PCC tracks the subjective value of faces, and not individual identity. Taken together, our data suggest that the PCC plays a key role in encoding the salient features of the environment and does so more strongly for social than gustatory stimuli. This lends credibility to the hypothesis that the default mode network of brain is exteroceptive, broad, and socially-oriented.

2. The posterior cingulate cortex tracks social value

2.1 Introduction

A role for the PCC has been posited in a number of diverse domains, including reward and outcome monitoring (Kable and Glimcher 2007), task engagement (Eichele et al 2008), and social cognition (Maddock et al 2001, Maddock et al 2003). Electrophysiological studies have implicated the PCC in signaling the subjective value of chosen options (Levy et al 2011, McCoy and Platt 2005), and strategy for switching behavioral choices (Hayden et al 2008, Pearson et al 2010). Furthermore, human imaging studies have suggested that the PCC responds to the affective value of faces. However, despite numerous studies implicating the PCC in social cognition in humans, there is a lack of neurophysiological data describing the response of PCC neurons to social stimuli. In this study, we look at PCC neuronal activity in response to socially relevant stimuli, namely the faces of familiar monkeys.

The first task we used – called the distraction task – was designed to allow the monkeys to freely view the faces of either dominant or subordinate males. Subjects were given a choice between a dominant face paired with a large or small juice reward, and a corresponding subordinate face paired with a large or small juice reward. Monkeys showed a preference for the faces of dominant animals, and they were willing to choose the smaller juice reward in order to do so. Previous studies (Deaner et al 2003, Klein et al

2005, Watson and Platt 2012) have demonstrated that subjects consistently differentiate between monkeys belonging to different social categories. They value the faces of dominant monkeys more than the faces of subordinate monkeys, as shown by their willingness to sacrifice fluid reward in order to view the faces of dominant animals. The distraction task was set up to recapitulate the behavior seen in the pay-per-view task. We analyzed the firing rates of neurons in the PCC while monkeys performed the distraction task.

2.2 Materials and Methods

2.2.1 Subjects

All procedures were in accordance with the guidelines established by Duke University's Institutional Animal Care and Use Committee and the Public Health Service's Guide for the Care and Use of Animals. The subjects were two male, adult rhesus macaques (*Macaca mulatta*) who were individually housed in a colony of 10 male macaques, all of whom had visual and auditory contact with each other. The subjects were fluid restricted outside of the experimental sessions.

2.2.2 Surgical procedures

Standard, sterile surgical techniques were performed. First, a head-restraining prosthesis (Crist Instruments) was implanted in subject monkeys. Subjects were allowed a 6-week recovery period, following which they were habituated to head-restraint and trained to perform occulomotor tasks for fluid reward. A second surgical procedure was

undertaken to place a stainless steel recording chamber (Crist Instruments) over the PCC at the intersection of the interaural and midsagittal planes. Animals were provided antibiotics and analgesics for 10 days following all surgical procedures. The chamber was kept sterile with regular antibiotic rinses and sealed using replaceable, sterile caps (Crist Instruments).

2.2.3 Behavioral techniques

The horizontal and vertical eye-positions of head-restrained subjects were sampled at 1000 Hz by an infrared eye-monitoring camera system (SR Research, Osgoode, ON). Visual stimuli were presented on a computer monitor placed approximately 40 cm in front of the subject and centered on his eyes. Stimulus presentation was controlled using Matlab (Mathworks, Natick, MA) along with Psychtoolbox (Brainard 1997) and Eyelink Toolbox (Cornelissen et al 2002).

The distraction task was a juice-choice task (Figure 2). The subjects were required to choose between two targets, the selection of which resulted in the delivery of juice. Volumes of juice differed between the two targets, one delivering a larger juice reward compared to the other. Upon successful completion of each trial, the juice reward was delivered to the subject by means of a tube. Juice delivery was controlled by a solenoid system, the amount of juice delivered depended on the amount of time for which the solenoid remained open and was measured in terms of 'solenoid open time' in ms.

Each trial had five epochs: acquisition of fixation, juice choice, face stimulus, reward delivery, and inter-trial interval . A trial was initiated by fixating on a central fixation square. Following acquisition of fixation, two eccentric targets were presented. The colors of the targets indicated the juice reward associated with them, each juice value being represented by a unique color. There were four possible juice choices offered to the subjects (100 ms versus 200 ms; 125 ms versus 175 ms; 135 ms versus 165 ms; 145 versus 155 ms). The juice targets were on screen for 500 ms, following which two face stimuli were presented. Placement of the face stimuli was such that both the faces and juice targets were simultaneously visible. Subjects had a 1000 ms free-viewing period, during which they were free to view either of the two faces or juice targets. The face stimuli presented were either that of dominant monkeys or subordinate monkeys. Thus there were four possible choices available to the subjects each trial: large juice reward/dominant face vs small juice reward/dominant face, large juice reward/dominant face vs small juice reward/subordinate face, large juice reward/subordinate face vs small juice reward/dominant face, and finally large juice reward/subordinate face vs small juice reward/subordinate face. At the end of the free-viewing period, juice reward was delivered to the subject based on the face and juice target he was looking at. On 10% of the trials, no face stimuli were presented. On these trials, subjects were only presented with the juice targets and were required to make a choice between juice reward values without the distraction of face stimuli.

When presented with only juice targets, subjects consistently chose the large juice reward over the small juice reward (Figure 3). However, when face stimuli were presented along with juice targets, choices made by the subjects were influenced by the presence of the face stimuli (Figure 4). This effect was only observed at 125 ms versus 175 ms of juice for Subject S, and 145 ms versus 155 ms of juice for subject B, and only these juice values were used for further electrophysiological study.

2.2.4 Face stimuli

A four megapixel camera (Nikon CoolPix 4600) was used to acquire all face stimuli. The images were of six monkeys that the two subjects were familiar with. Using unidirectional submissive gestures, three were judged to be dominant to the two subject monkeys and three were judged to be subordinate. Only neutral facial images were used, with varying eye gaze and head direction. Around 500 - 1000 images were used for each of the six monkeys. The heads were cropped and matched for size and luminance. The identities of the two face stimuli to be presented to the subjects were chosen at random.

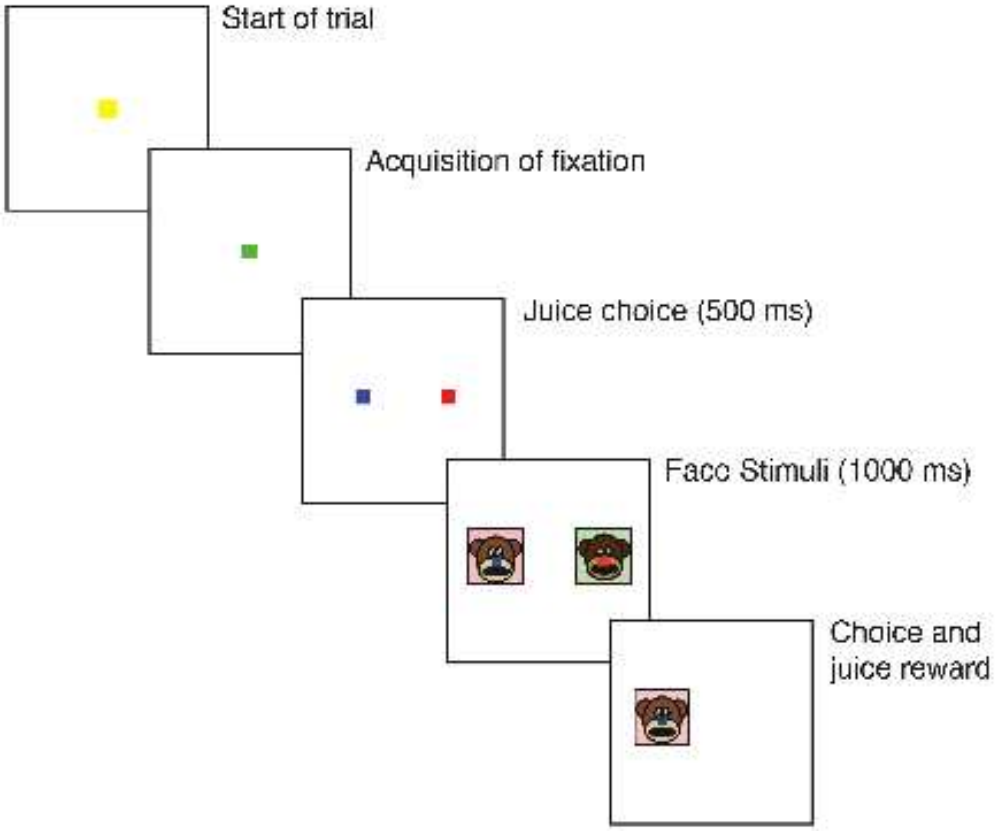

Figure 2: Task Design. The start of a trial was marked by the appearance of a central yellow fixation square. Once subjects had acquired fixation, as indicated by a color change to green, the fixation target disappeared and two eccentric juice targets were presented on screen. The color of the target indicated the juice reward associated with it. After 500 ms, two face stimuli were presented on screen. Subjects had 1000 ms to view either of the two face stimuli. Following this free-viewing period, a juice reward was delivered to the subjects based on the image/juice target the subject was looking at.

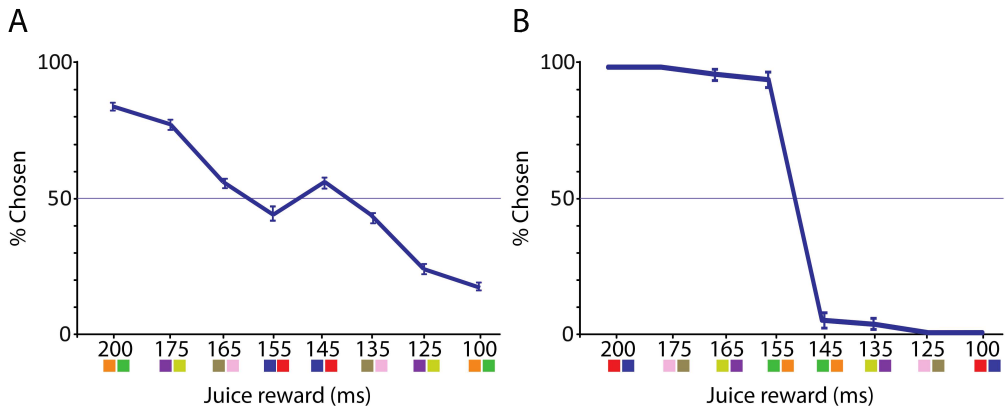

Figure 3: Subjects prefer large juice rewards to small juice reward. When offered a choice between a large juice reward or a small juice reward, both subjects (S and B) preferred large juice rewards. For subject S, the minimal discriminable juice level (i.e. the smallest difference between the two juice options that elicited preference for larger juice) was 125 ms versus 175 ms (A), while the minimal discriminable level for subject B was 145 ms versus 155 ms (B). (Data are presented as mean ± SEM)

2.2.5 Microelectrode recording techniques

We recorded single unit activity from 179 neurons of two subject monkeys (Subject S: 147, Subject B: 32) while they were engaged in performing the distraction task. Single electrodes (Frederick Haer Co) were lowered into the PCC under the guidance of a microdrive system (Kopf). Individual action potentials were identified and isolated using a Plexon System (Plexon Inc., Dallas, TX). Criteria for inclusion of neurons in the study was based on quality of isolation only, and not on task-responsiveness.

The PCC was identified using stereotaxic measurements. Neuronal recordings were made in areas 23 and 31, equivalent to those reported previously (Dean and Platt 2006; Hayden et al 2008; Hayden et al 2009; McCoy et al 2003; Pearson et al 2009).

2.2.6 Analysis

An alpha of 0.05 was used as criterion for significance. Peri-stimulus time histograms (PSTHs) were constructed by aligning spikes from successful trials (those that resulted in juice delivery) to stimulus presentation. Neuronal firing was averaged across trials. Firing was binned into the following epochs: juice choice (500 ms), face stimulus (1000 ms), reward (500 ms following reward delivery), inter-trial interval ITI (a 500 ms bin preceding start of each trial). Statistical analyses were performed on the binned firing rates. All analyses were undertaken using Matlab (Mathworks, Natick, MA).

2.3 Results

2.3.1 Monkeys exhibit stable preferences for faces depending on social status

Subjects performed approximately 1000 completed trials of the distraction task daily and were required to shift gaze to one of two eccentric targets. Subjects had to chose between pairs of options drawn from all combinations of two possible juice rewards and two different dominance classes of face stimuli. Depending on the juice reward and face stimulus presented, subjects could chose between: a) a large juice reward and a dominant face versus a small juice reward and a dominant face; b) a large juice reward and a dominant face versus a small juice reward and a subordinate face; c) a large juice reward and a subordinate face versus a small juice reward and a dominant

face; d) a large juice reward and a subordinate face versus a small juice reward and a subordinate face.

When presented with only juice reward targets, subjects preferred the large juice reward (Percent of trials the subjects chose the large juice reward: M = 78% $\pm$ 2.7; Figure 4A). The presence of face stimuli significantly altered this juice choice behavior of subjects (Figure 4A). When presented with a choice of a large juice reward associated with a dominant face, this preference for a large juice reward did not change irrespective of the face stimulus associated with the small juice reward (small juice reward with dominant face: M = 80.71% $\pm$ 3.33; small juice reward with subordinate face: M = 77.5% $\pm$ 4.5). When presented with a choice of a large juice reward and a subordinate face versus a small juice reward and a subordinate face, subjects still preferred the large juice reward (M = 75.6% $\pm$ 7.1). However, when presented a choice between a large juice reward with a subordinate face and a small juice reward with a dominant face, subjects preferred the large juice reward significantly less (2 way ANOVA, Significant interaction effect between face category and juice choice, $F = 4.33$, $p = 0.03$, M = 51.9% $\pm$ 4.1). Subjects preferentially looked away from subordinate faces towards dominant faces, and were willing to sacrifice juice reward in order to do so. Thus, subjects differentially valued faces of other monkeys based on social status, consistent with previous studies (Deaner et al 2005).

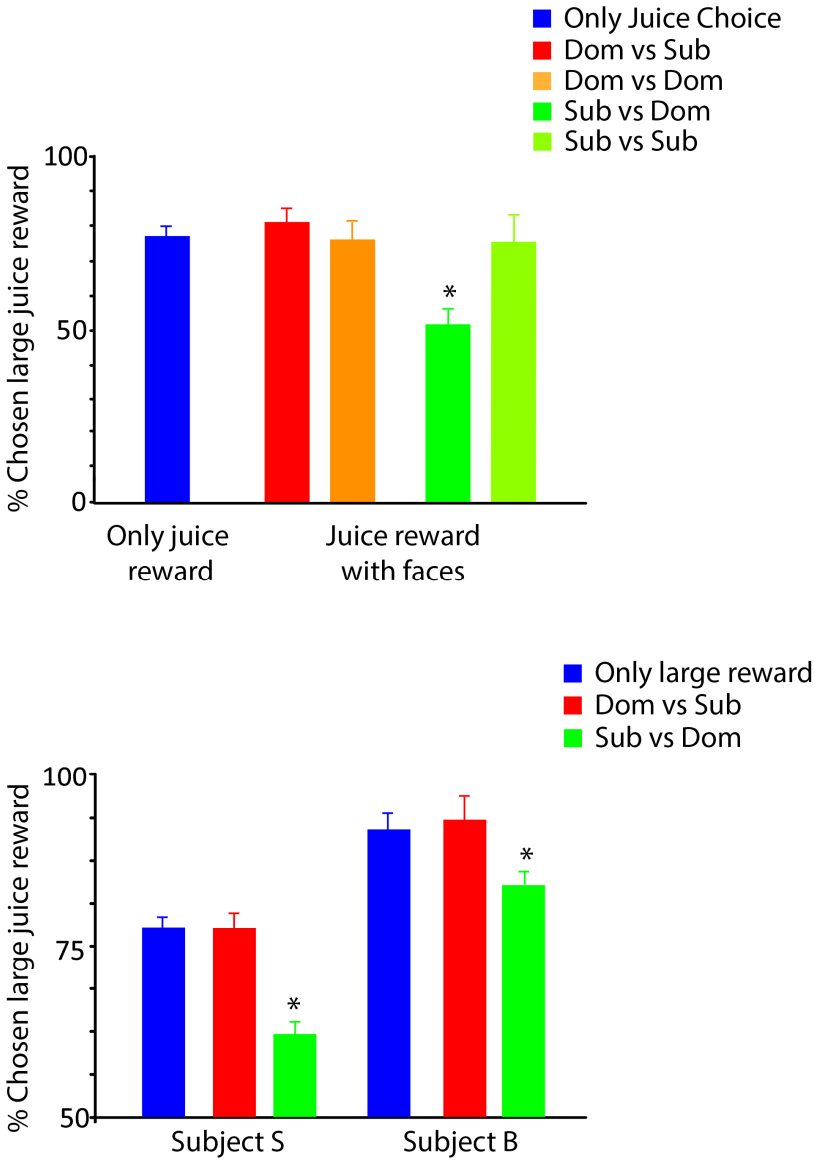

Figure 4: Subjects preferentially chose high juice rewards and faces of dominant monkeys.

(A) Subjects preferred large juice rewards except in cases where a subordinate face was associated with larger juice amount and a dominant face associated with smaller juice amount, in which case subjects looked away from the large juice reward (dark green). (B) This switch from a large juice reward and subordinate face and towards a small juice reward and dominant face was observed in both subjects (S and B). (Data are mean ± SEM, * $p < 0.05$)

2.3.2 Neuronal firing rates in the PCC track social category of face stimuli

We examined the responses of neurons in the PCC to the choices each subject made. Figure 5 shows an example cell with neuronal firing rate in response to the juice reward and face stimulus choice made by the subject. This neuron clearly tracks the face stimulus the monkey is looking at and not the juice reward choice, with higher firing for subordinate faces as compared to dominant faces. This effect was also observed at the level of the population (Figure 6A), with average population activity of the studied neurons being higher when the subject was observing subordinate faces as opposed to dominant faces.

Of the 179 neurons collected, 41.9% of cells (n = 75) responded differentially to the face stimulus depending on its social status. A significant difference in firing rate was observed in the face stimulus epoch where subjects looked at the faces of either dominant or subordinate monkeys, and in the 500 ms bin post delivery of reward. Of these face-responsive cells, 61.33% (n = 46) fired significantly more for subordinate faces and 38.67% (n = 29) fired significantly more for dominant faces (see Figure 6C). The average firing rate of population during the face stimulus and reward delivery epochs showed significantly greater activity for subordinate faces (firing rate: M = 2.175 Hz $\pm$ 0.27) as compared to dominant faces (M = 2.82 Hz $\pm$ 0.36) (two-tailed t-test, $t = 3.6$, $p < 0.05$; Figure 6B). None of the 75 cells showed differential firing activity depending on the

juice reward the subject received.

We also assessed whether the presence of the second face stimulus altered the neuronal response within the PCC. The firing rate of cells reflected the face stimulus the subject chose to look at, irrespective of the second face stimulus it was paired with (Figure 6B, see the right-hand bar graphs). The firing rates of neurons were smaller when subjects were viewing dominant stimuli, irrespective of whether the second stimulus was of a dominant (dark red bar; firing rate: M = 2.05 Hz $\pm$ 0.23) or subordinate face (light red bar; firing rate: M = 2.267 Hz $\pm$ 0.33). Correspondingly, the firing rates of neurons increased when subjects were viewing subordinate faces, irrespective of whether the second stimulus was of a dominant (dark green bar; M = 3.167 Hz $\pm$ 0.67) or subordinate face (light green bar; M = 2.77 Hz $\pm$ 0.55) (2-way ANOVA, $F = 7.25$, $p = 0.03$).

Subjects could freely view both targets during the juice target epoch and during the face stimulus epoch. Thus, they were free to switch between target choices between the two epochs. This switching behavior was most prominently displayed when subjects looked away from a large juice reward to look toward dominant monkey face associated with small juice reward. Firing of neurons in the PCC has been linked to both saccade-related activity (McCoy et al 2003) and switching behavior (Hayden et al, 2008), so we assessed whether firing rates of neurons were affected by a switch between the juice target and face stimuli. The firing rates of neurons were not modulated by any previous saccade-related switch activity, and only reflected the face stimulus the subject was

currently looking at. (2-way ANOVA, no main or interaction effect between stimulus category and stay/switch strategy, $F = 0.11$, $p = 0.9$).

Thus, the vast majority of the task responsive cells showed differential firing activity based solely on the social status of the face stimulus the subject was observing. On average, the firing activity of these cells was significantly greater for subordinate faces as compared to dominant faces.

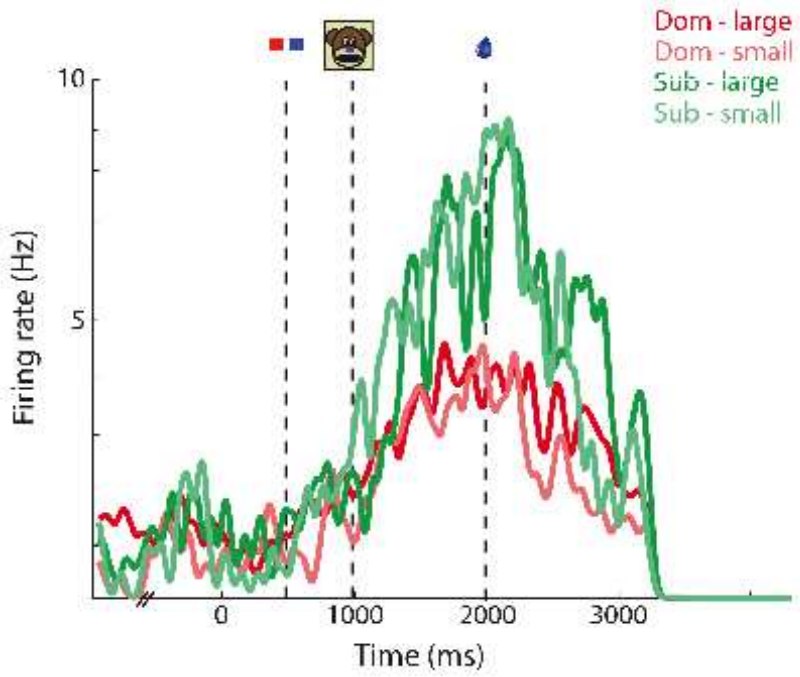

Figure 5: Firing rate of a single PCC neuron is modulated by the social status of the face the subject is looking at.

The PSTH shows the firing activity of a single example neuron in response to the juice reward and face stimulus choice the subject makes. The cell shows significantly greater firing for subordinate faces as compared to dominant faces, irrespective of the juice reward chosen.

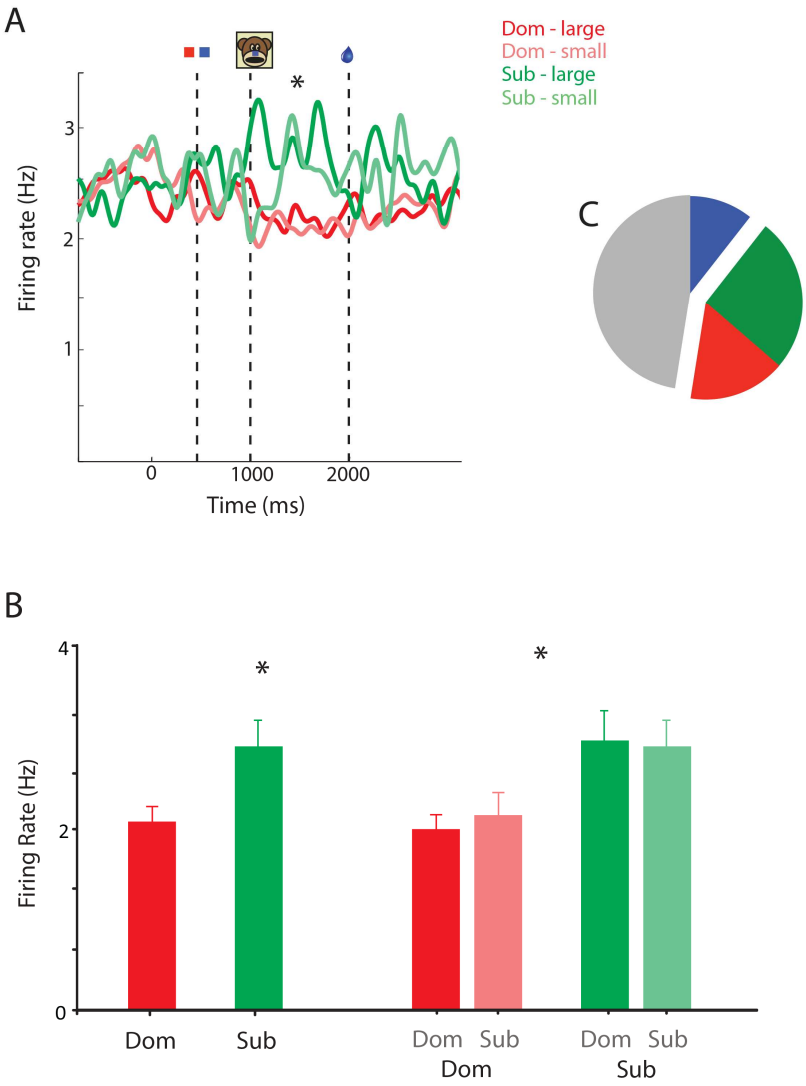

Figure 6: Population firing rate of PCC neurons is modulated by the social status of the face the subject is looking at

(A) The PSTH shows the average firing rate of neurons in response to the juice reward and face stimulus choice the subject makes. (B) The population firing rate of neurons averaged over the face stimulus and reward delivery epochs. The population averaged activity only signals the image choice the monkey makes, but not the juice reward and the second face stimulus. (C) Representation of stimulus-responsiveness of neurons. 25.3% of all neurons show higher firing for subordinate faces (green), while 16.2% show higher firing for dominant faces (red). (Data are mean ± SEM, * p <0.05)

2.3.3 Neuronal firing rates in the PCC track social category and not individual identity

The distraction task required subjects to chose to look at either a dominant face or a subordinate face. There were three monkeys in each social category, making a total of six monkeys that the subject could look at. However, the possibility remains that the neurons' social category responsiveness is driven by individuals. Figure 7A shows this is not the case. There the choices made by subject are separated not only by social status of the face (dominant or subordinate), but also by individual identity of the face (Dominant monkeys: Sh, O, E and subordinate monkeys: L, H, Y). An ANOVA revealed a significant main effect of social status ($F = 20.6$, $p < 0.01$) only.

This categorization is also reflected at the level of the firing activity of neurons. Figure 7B shows the population firing rate of neurons based on social category and individual identity. A significant increase in firing activity was observed for all subordinate faces, with a main effect of social status and no effect of individual identity (2-way ANOVA, $F = 10.21$, $p < 0.05$).

Thus, it appears that in the context of the distraction task, subjects categorized the faces of other monkeys based on social status in a binary fashion as dominant or subordinate, while ignoring individual identities. Furthermore, this categorization was reflected at the level of firing activity of neurons in the PCC. Cells in the PCC fired significantly more for subordinate monkey faces as compared to dominant faces.

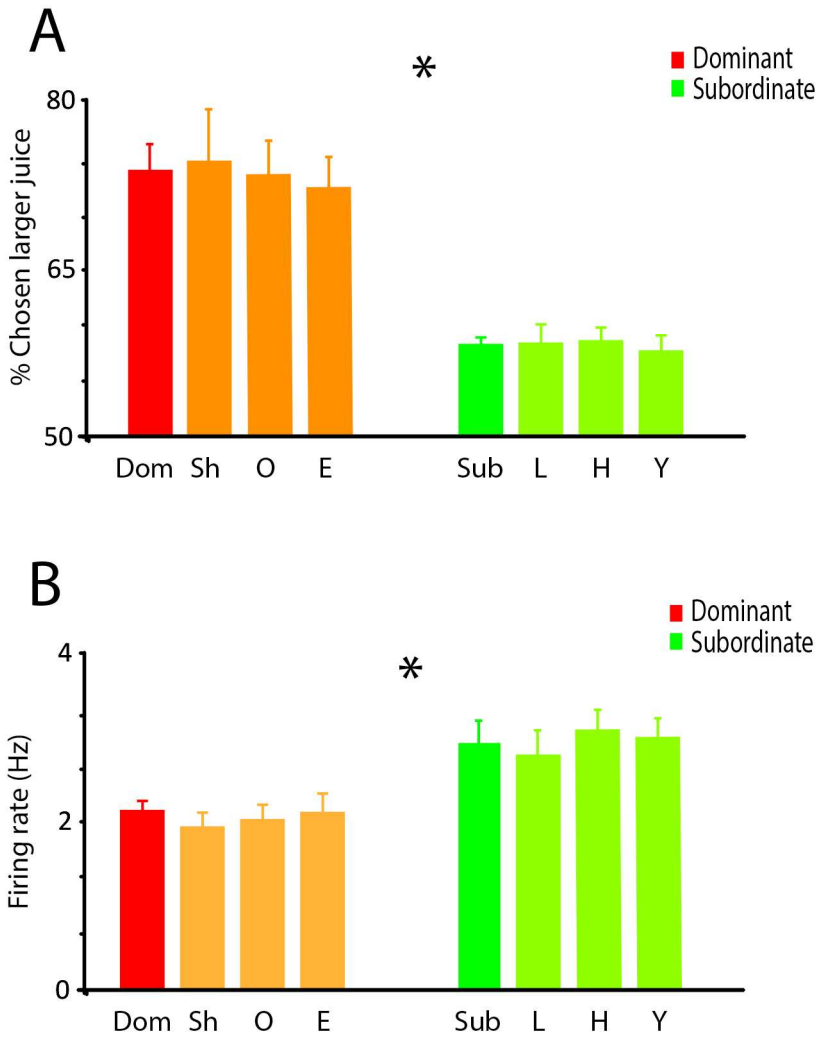

Figure 7: Subjects categorize monkey faces based on social status and not individual identity

(A) Subjects chose a large juice reward less frequently when it was associated with a subordinate monkey face. There was a main effect of social status, and no effect of individual identity. (B) Firing activity of the population of PCC neurons reflects the categorization of monkey faces based on social status. Cells fired more for subordinate monkey faces as opposed to dominant faces. Only a significant main effect of social status was seen. (Data are mean + SEM, 8 < 0.05)

2.3.4 Neuronal firing rates in the PCC do not track juice reward choice

In contrast to the 41.9% of neurons signaling social category, only 10.6% (n = 19) of neurons (n = 19) showed differential firing activity in response to the juice choice made by the subject (see Figure 6C, blue). Only 11 neurons of the 179 sampled showed greater firing when the subject chose a large juice reward, while only 7 neurons showed greater firing when the subject chose a small juice reward. When averaged across the entire population of 19 juice choice-responsive neurons, there was no significant effect of juice choice on the firing activity of neurons. (2-way ANOVA, $F = 0.3$, $p > 0.6$)

Of the 179 neurons collected in this study, 52.5% responded to stimuli presented in the task. Of these task-responsive neurons, the vast majority were preferentially responsive to face stimuli and not to juice reward. This is in contrast to previous studies where significant numbers of juice reward-responsive cells were found in comparable regions of the PCC (McCoy et al, 2003, McCoy and Platt 2005).

Of the 94 task-responsive cells, 79.8% of cells responded differentially to face stimuli (n = 75), and only 20.2% of cells showed differential firing activity to the juice choice (n = 19). Out of the entire population, an insignificant number of neurons (n = 2), responded significantly to both the face stimuli and the juice choice. Thus, the population of task-responsive neurons in this study appear to signal the social status of the face the subject is looking at.

2.3.5 Neuronal firing rates in the PCC predict errant behavior in subsequent trial

The PCC is believed to be involved in monitoring the environment as opposed to facilitating focused attention. In keeping with this, previous reports demonstrate that neuronal activity in the PCC is anti-correlated with task engagement, and that the level of task engagement (as measured by reaction times and incomplete trials) is predictable based on spontaneous neuronal activity prior to commencement of each trial (Hayden et al, 2009). We analyzed neuronal activity during the inter-trial interval preceding each trial (a 500 ms bin prior to the start of every trial) to see whether it predicted future performance.

We first probed whether firing rate of neurons predicted task engagement as indexed by errors. An error trial was one in which the subject broke fixation by prematurely looking away from the central fixation square. This was observed in approximately 19% of trials that a subject performed daily. On average, firing during the ITI epoch preceding the start of a trial was significantly higher for error trials (Student's t-test, $p < 0.03$, firing rate preceding correct trials: mean = 1.98 Hz $\pm$ 0.05; firing rate preceding error trials: mean = 1.67 Hz $\pm$ 0.21, Figure 8A). Thus, in keeping with previous results, the spontaneous firing rates of neurons preceding the start of every trial indicated the level of task engagement as measured by errors made.

It has also been reported that spontaneous neuronal activity within the PCC

predicts whether the subjects will switch from one choice to another in a simple two-choice task (Hayden et al, 2008). We thus asked whether the neuronal activity in the ITI predicted whether subjects would make the same choice as the previous trial (a 'stay' strategy) or change choice (a 'switch' strategy) (Figure 8C). In contrast to previously published results, the firing of neurons during the ITI did not predict the strategy adopted by subjects on the subsequent trial (Mean firing rate when subjects viewed dominant faces then decided to stay: 2.14 Hz $\pm$ 0.47 or switch: 2.07 Hz $\pm$ 0.73; Mean firing rate when subjects viewed subordinate faces then decided to stay: 2.02 Hz $\pm$ 0. 77 or switch: 2.2 Hz $\pm$ 0.77, 2x2x2 ANOVA, $p = 0.8$). Additionally, firing during the ITI did not predict whether the monkey would choose to view a dominant face or a subordinate face on the subsequent trial (Mean firing activity prior to viewing dominant face: 2.2 Hz $\pm$ 0.2 and subordinate face: 2.18 $\pm$ 0.33; $p > 0.5$; Figure 8B). Thus, spontaneous firing activity of PCC neurons preceding the start of trials predicted the task engagement of subjects, as indexed by errors made, but did not signal future choice behavior.

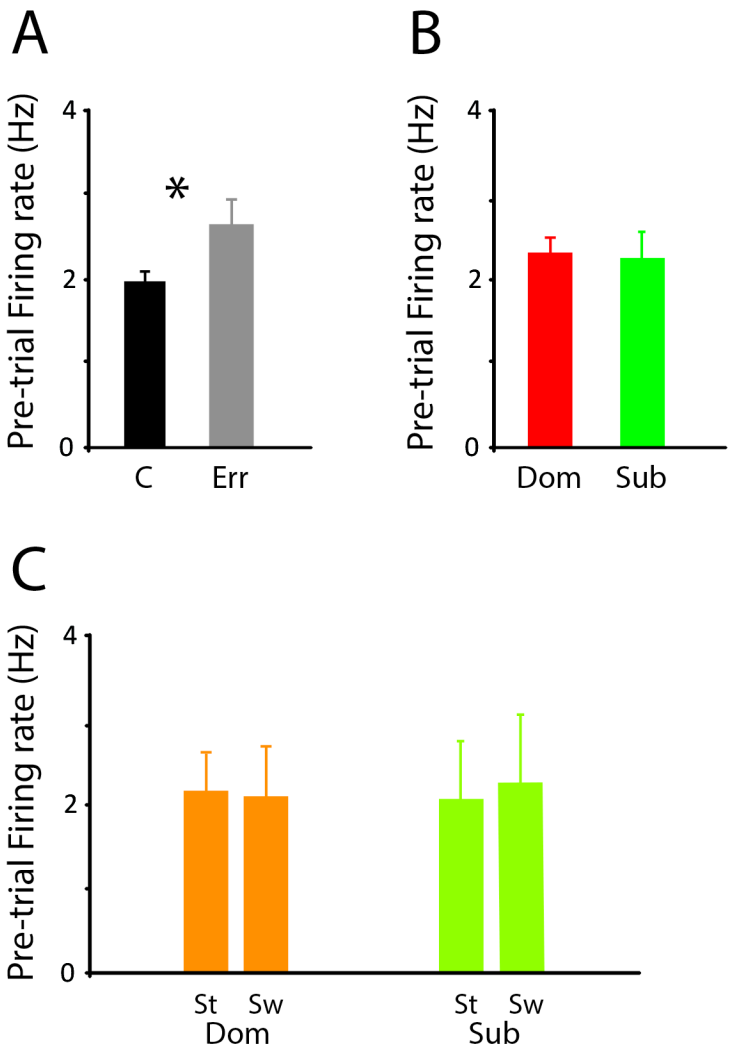

Figure 8: PCC neurons predict task performance

(A) Firing rate of neurons in a 500 ms ITI epoch preceding the start of a trial. Spontaneous neuronal activity was greater preceding an error trial. Firing rate of neurons in a 500 ms ITI epoch preceding the start of a trial did not predict the face stimulus choice (B) or the stay-switch strategy (C) on subsequent trials. (Data are presented as mean ± SEM, * $p < 0.05$)

2.3.6 Face stimuli and task engagement

We assessed whether the choice made on current trials affects subsequent choices by performing a two-way ANOVA with juice and face choice on the current trial as factors, and choice behavior on the subsequent trial as outcome. No main or interaction effect of current juice reward or face stimulus was found on choice behavior on the subsequent trial ($F = 0.23$, $p > 0.5$). Thus, the subjects appeared to be treating each trial independently of the previous trial.

To further explore whether current choice had an influence on future behavior, we also analyzed whether choices made on current trials affected task engagement as measured by error trials. Error trials were classified as trials that were aborted due to subjects prematurely looking away from the central fixation target. An ANOVA revealed that there was no effect of juice choice or face stimulus on task engagement on subsequent trials ($F = 0.1$, $p = 0.76$). Additionally, we also looked at the history of choices to see whether it influenced task engagement. That is, whether repeated exposure to a particular face stimulus (either dominant or subordinate) or juice reward (either small juice reward or large) affected task engagement. Significantly, we found that repeated exposure to subordinate faces increased the likelihood of error trials (Figure 9, ANOVA, post-hoc Student's t-tests, $p < 0.05$).

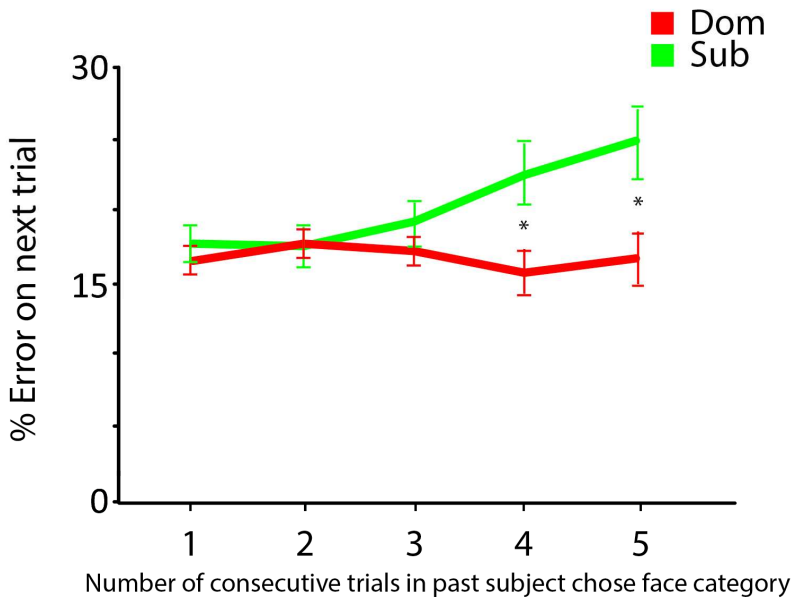

Figure 9: Social status of face stimulus affects task engagement

The face stimulus a subject observed during previous trials affect task engagement as indexed by error trials. The successive viewing of a subordinate face increased the likelihood of error trials, indicating a decrease in task engagement (Data are mean + SEM, * $p < 0.05$)

2.4 Conclusion

Macaque monkeys differentially value face images depending on the social categories they belong to. They are even willing to sacrifice a small amount of juice reward in order to look at dominant faces as opposed to subordinate ones. This has been previously reported using a monkey "pay-per-view" task (Deaner et al 2005), and is further substantiated using our distraction task in the present investigation. Critically, within the constraints of the distraction task, monkeys seem to classify faces in a binary fashion as either dominant monkeys or as subordinate monkeys.

Consistent with behavior, neurons in the PCC seem to predominantly encode the dominance status of the face a monkey chooses to view. The greatest proportion of task responsive cells (48.9%) show higher firing rates when monkeys view subordinate faces as opposed to dominant faces, though a substantial proportion (30.9%) were modulated in the opposite direction, showing higher firing activity for dominant faces. At the level of population firing rate, the averaged firing rate of all task-responsive neurons in the PCC showed significantly higher firing for subordinate faces as opposed to dominant faces. Intriguingly, social stimulus appears to have privileged access to the PCC. Previous studies of single unit activity within the PCC showed robust activations in response to juice-only reward choices (McCoy et al 2003, Hayden et al 2008, Pearson et al 2010). However, in our paradigm, only 20.2% of task-responsive cells showed differential firing to juice choices. This is dwarfed by the 79.8% of task-responsive cells that showed preferential firing for faces. Thus, social value appears to be more broadly and strongly represented in the PCC than those of juice rewards.

Firing activity within the PCC also precedes changes in behavioural strategy in both a simply choice task (Hayden et al 2008) and in a complex dynamic foraging (Pearson et al 2009), and microstimulation within the PCC results in subjects switching behavioural strategies (Hayden et al 2008). Thus, activity within the PCC precedes and predicts a change in behavioural strategy. However, this was not borne out in the distraction task. Activity of neurons did not indicate a change in choice strategy, either

between juice choice and social stimulus choice, or between trials. While this might be considered surprising, especially given the causal role for the PCC in strategy switching, the task design between the current task and previous tasks might prove crucial in explaining the altered behavior of neurons. The distraction task requires monkeys to make a choice between two fixed juice rewards, a cognitively unchallenging demand. Furthermore, each trial was independent of the previous trials. The earlier studies involved more complex decisions, necessitating constant learning, tracking of outcomes and updating of the value of the juice options (Pearson et al 2009). This increased cognitive load might necessitate the recruitment of the PCC, this being unnecessary for the distraction task.

To conclude, neurons in the PCC seem to primarily carry information about the social status of the monkey currently being observed and this is at the cost of information regarding the reward delivery.

3. The posterior cingulate cortex tracks social value and not individual identity

3.1 Introduction

Monkeys value faces differentially depending on the social categories they belong to (Deane et al 2003, see chapter 2). Furthermore, this differential valuation of faces is reflected at the level of neuronal firing in the PCC, with the population of cells showing consistently higher firing for subordinate faces as opposed to dominant faces. Furthermore, subjects appear to classify the faces of monkey in a binary fashion as either dominant or subordinate status faces, and this is also seen in the firing rate of neurons. The firing of PCC neurons reflect the social status of the face, but not its overt identity. Finally, the majority of task-relevant neurons signal information regarding the social category of the face stimulus as opposed to fluid reward and trial outcome (McCoy and Platt 2003, McCoy et al 2005, Hayden et al 2008).

An interesting point to note is that the face stimulus in the distraction task is a task-irrelevant (i.e. independent of obtaining juice reward). The task involves maximization of received fluid reward, and the dominance status of the face stimulus is not indicative of the size of subsequent juice reward. The distraction task looks at the implicit attention monkeys pay to each other based on their dominance status, and the value attached to faces relies on the inherent, untrained attractiveness of dominant faces over subordinate ones. Monkeys seem to classify faces in a binary fashion as either

dominant or subordinate. Importantly, the activity of PCC neurons also tracks the social category of stimuli in a binary fashion, and does not signal explicit identity.

It is possible that while PCC neurons do not track identity information in a task that does not call for explicit recognition of faces, they do so if it was relevant to task performance. The match-to-identity task requires subjects to correctly recognize the identity of individual monkeys. Furthermore, the fluid reward is critically linked to the individual identity of faces, since the absence of a fluid reward provides valuable feedback on the accuracy of task performance. Subjects in the match-to-identity task are thus best served by closely monitoring both the individual identities of faces (irrespective of their social status) and the fluid outcome of each trial.

We recorded neuronal activity from the PCC while subjects performed the match-to-identity task. Given that the neurons in the PCC have been shown to be highly responsive to fluid rewards (McCoy and Platt 2003, McCoy et al 2005, Hayden et al 2008) and omission of fluid rewards (McCoy et al 2005), we studied whether these neurons would encode trial outcome, especially when trial outcome supplied critical information about the social information in the task (i.e. whether a correct identification was made). If PCC cares solely about the subjective value of faces, as indicated by the distraction task, the firing activity of neurons should again track the social status of face stimuli as opposed to individual identity and fluid reward, even when the identity and reward are

critical and relevant to task completion respectively.

3.2 Materials and Methods

3.2.1 Subjects

All procedures were in accordance with the guidelines established by Duke University's Institutional Animal Care and Use Committee and the Public Health Service's Guide for the Care and Use of Animals. The subjects were two male, adult rhesus macaques (*Macaca mulatta*) who were individually housed in a colony of 10 male macaques, all of whom had visual and auditory contact with each other. The subjects were fluid restricted outside of the experimental sessions.

3.2.2 Surgical procedures

Standard, sterile surgical techniques were performed. First, a head-restraining prosthesis (Crist Instruments) was implanted in subject monkeys. Subjects were allowed a 6-week recovery period, following which they were habituated to head-restraint and trained to perform occulomotor tasks for fluid reward. A second surgical procedure was undertaken to place a stainless steel recording chamber (Crist Instruments) over the PCC at the intersection of the interaural and midsagittal planes. Animals were provided antibiotics and analgesics for 10 days following all surgical procedures. The chamber was kept sterile with regular antibiotic rinses and sealed using replaceable, sterile caps (Crist Instruments).

3.2.3 Behavioural techniques

The horizontal and vertical eye-positions of head-restrained subjects were sampled at 1000 Hz by an infrared eye-monitoring camera system (SR Research, Osgoode, ON). Visual stimuli were presented on a computer monitor placed approximately 40 cm in front of the subject and centered on his eyes. Stimuli presentation was controlled using Matlab (Mathworks, Natick, MA) along with Psychtoolbox (Brainard 1997) and Eyelink Toolbox (Cornelissen et al 2002).

Subjects were trained on a 'match-to-identity' task, in which they were required to correctly identify monkeys (Figure 10). The subjects were shown a sample monkey image and subsequently presented two target images. One target image was a different picture of the sample monkey, the second target being a distractor monkey. Subjects were required to correctly identify the monkey in the sample image and indicate their choice by making an eye movement to the correct target image. Upon successful completion of each trial, the juice reward was delivered to the subject by means of a tube. Juice delivery was controlled by a solenoid system, the amount of juice delivered depending on the solenoid open time and measured in terms of 'solenoid open time' in ms.

Each trial contained five task-defined epochs: acquisition of fixation, sample image, target images, reward delivery, and inter-trial interval. A trial was initiated by fixating on a central fixation square. Following acquisition of fixation, subjects were allowed to freely view a central sample image for 750 ms. Following the sample image

presentation, two eccentric target images were presented. Additionally, two target squares were displayed below the target images, and the subject indicated his choice by making an eye movement to one of the target squares. Subjects had a total of 1500 ms in which to freely view both target images and indicate a choice. A correct choice was rewarded with a juice reward (150 ms), while an incorrect choice resulted in no juice reward.

3.2.4 Face stimuli

A four megapixel camera (Nikon CoolPix 4600) was used to acquire all face stimuli. The images were of six monkeys that the two subjects were housed with. Using unidirectional submissive gestures, three were judged to be dominant to the two subject monkeys and three were judged to be subordinate. Only neutral facial images were used, with varying eye gaze and head direction. A few hundred images were used for each of the six monkeys. The heads were cropped and matched for size and luminance. The identities of two monkeys to be presented to the subjects were chosen at random.

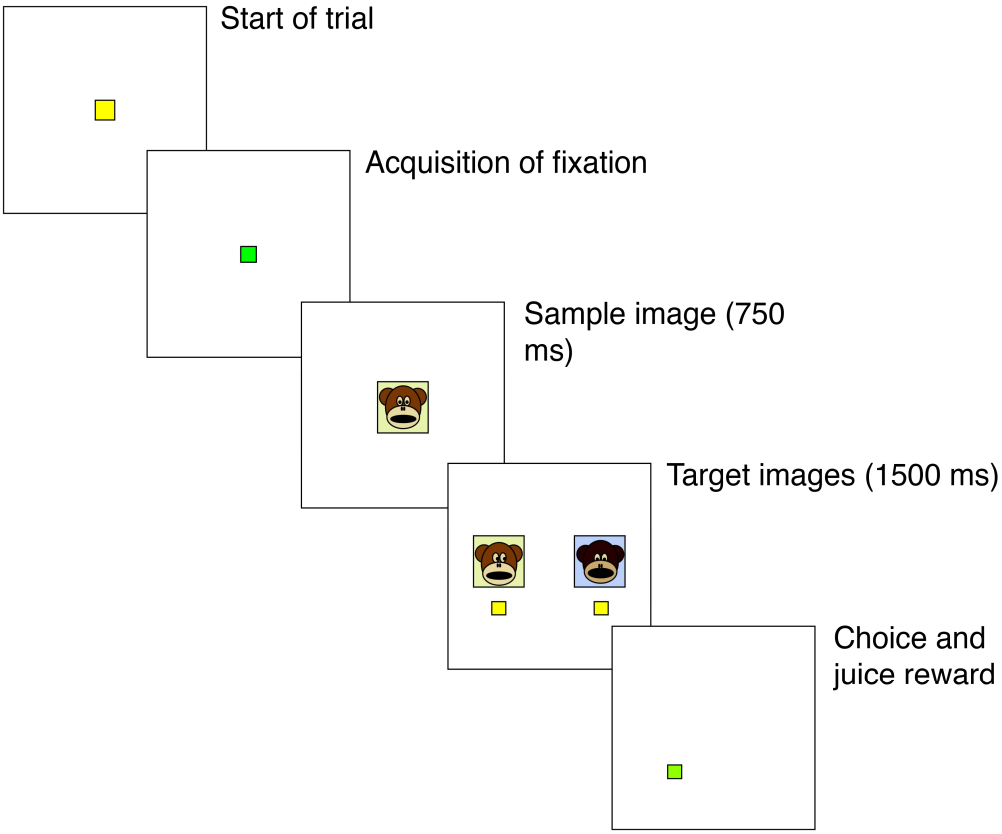

Figure 10: Task Design

The start of a trial was marked by the appearance of a central yellow fixation square. Once subjects had acquired fixation, as indicated by a change in color of the fixation square, the fixation target disappeared and a central sample image was displayed. After 750 ms, two target face stimuli were simultaneously presented on screen. Subjects had 1500 ms to view either of the two face stimuli. Within this free-viewing period, subjects had to saccade to one of the two yellow squares to indicate a choice. The image of the sample monkey used was changed between the initial sample presentation epoch and the subsequent target image epoch. Thus, subjects were not performing a simple sensory matching task. A choice was indicated by making an eye movement to one of the two targets below the face images. A juice reward was delivered to the subjects only following the correct identification of the monkey in the sample image.

3.2.5 Microelectrode recording techniques

We recorded single unit activity from 59 neurons from the two subject monkeys (Subject S: 27, Subject B: 32). Single electrodes (Frederick Haer Co) were lowered into the PCC under the guidance of a microdrive system (Kopf). Individual action potentials were identified and isolated using a Plexon System (Plexon Inc., Dallas, TX). Criteria for inclusion of neurons in the study was based on quality of isolation only, and not on task-responsiveness.

The PCC was identified using stereotaxic measurements. Neuronal recordings were made in areas 23 and 31, equivalent to those reported previously (Dean and Platt 2006; Hayden et al 2008; Hayden et al 2009; McCoy et al 2003; Pearson et al 2009).

3.2.6 Analysis

An alpha of 0.05 was used as criterion for significance. Peri-stimulus time histograms (PSTHs) were constructed by aligning spikes from successful trials (those that resulted in juice delivery) to stimulus presentation. Neuronal firing was averaged across trials. Firing was binned into the following epochs: sample image (750 ms), target image (1500 ms), juice reward (500 ms following resolution of choice), and inter-trial interval ITI (a 500 ms bin prior to start of a trial). Statistical analyses were performed on the binned firing rates. All analyses was undertaken using Matlab (Mathworks, Natick, MA).

3.3 Results

3.3.1 Subjects recognize and attend equally to other monkeys, irrespective of social status

Subjects performed approximately 700 trials of the match-to-identity task daily. They were required to correctly identify the monkey in the sample image and match it to one of the two target images, one target image being of the sample monkey and the second being a distractor monkey. Subjects had a maximum of 1500 ms to freely view both target images. They indicated their choice by shifting their gaze to target squares placed below the target images, and their reaction times and accuracy were measured. Both subjects could accurately identify sample monkeys.

Data were analyzed to determine whether subjects showed differential matching ability for dominant versus subordinate monkeys. Subjects could accurately identify both dominant and subordinate sample monkeys (% correct for dominant faces: M = 83% $\pm$ 0.35; % correct for subordinate faces: M = 81.75% $\pm$ 0.75; Figure 11, Student's t-test; $p = 0.41$). There was no significant interference in accuracy based on whether the distractor monkey was a dominant or a subordinate (% correct with dominant distractor: M = 85.97% $\pm$ 1.32; % correct with subordinate distractor: M = 81.26% $\pm$ 0.28; Figure 11, Student's t-test, $p = 0.34$).

Additionally, we also assessed whether subjects were equally attentive to dominant and subordinate sample monkeys, as indexed by the time it took to make

correct identifications (reaction times) and the pupil size of the subjects while observing either a dominant sample monkey or a subordinate one. Pupil size has long been established as an indicator of the value of visual stimuli, with increased pupil size being seen in response to emotionally-salient stimuli (Hess and Polt 1960). Furthermore, differences in pupil dilation also track the dominance status of monkey faces in a free-viewing task, with increased pupil size being observed following exposure to a dominant face (Watson et al 2009). Subjects attended equally to both dominant and subordinate sample monkeys. The reaction times for matching dominant samples (M = 580 ms $\pm$ 27) and subordinate samples (M = 573 ms $\pm$ = 24) did not differ significantly (Student's t-test, p = 0.08, Figure 12A). Subjects did show slower reaction times when they incorrectly identified sample images, but there was only a main effect of accuracy ($F = 3.12$, $p = 0.043$), and no effect of social status on reaction times (reaction time for incorrectly matching dominant sample: M = 670 ms $\pm$ 98, subordinate: M = 710 ms $\pm$ 55, $p > 0.08$).

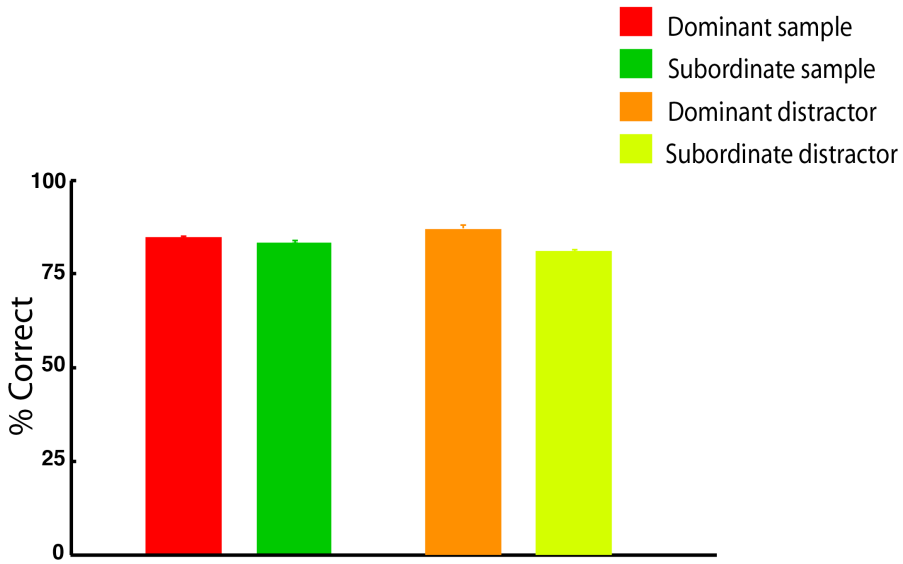

Figure 11: Accuracy in match-to-identity task

Subjects could correctly identify both dominant and subordinate monkeys, irrespective of whether the distractor monkeys were dominant or subordinate monkeys. (Data are represented as mean ± SEM)

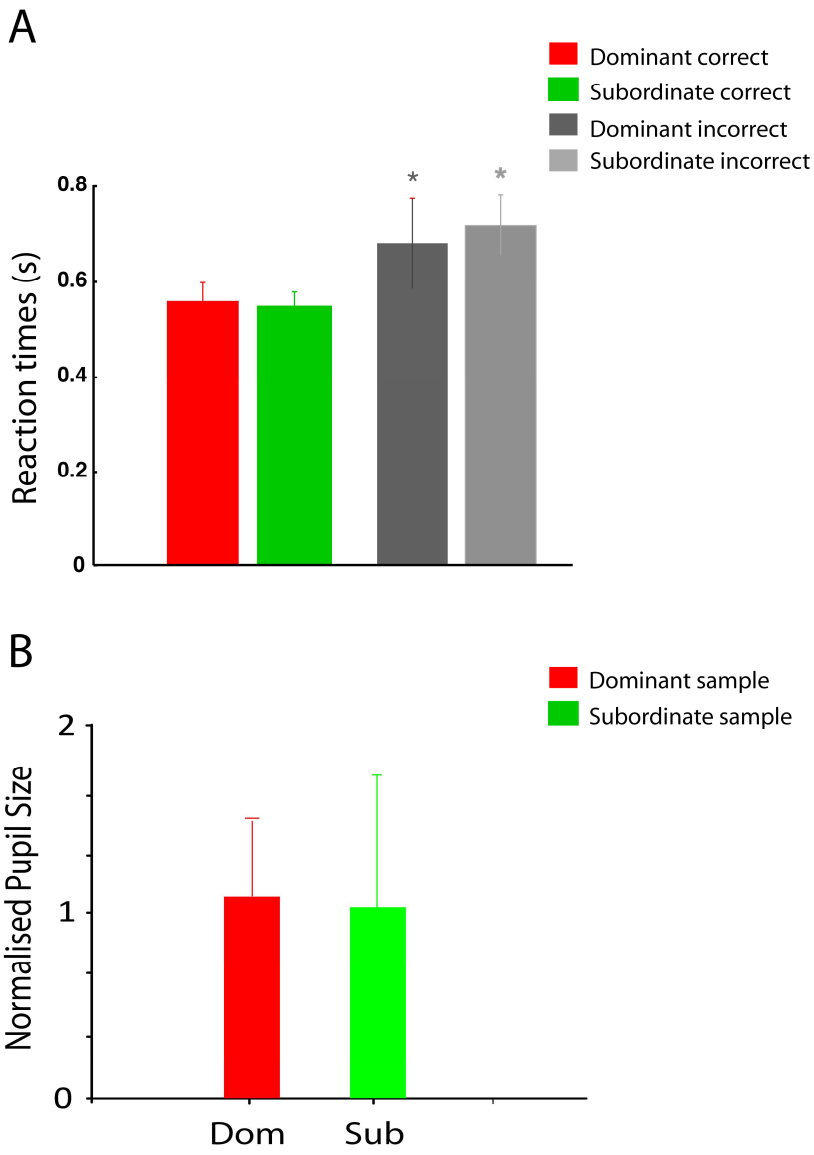

Figure 12: Subjects attended equally to dominant and subordinate sample images

(A) Subjects showed no difference in reaction times while matching dominant or subordinate monkeys. They were significantly slower on incorrect trials, but there was only a statistically significant main effect of trial outcome. (B) Subjects showed no difference in pupil size while viewing dominant or subordinate sample images. (Data are mean ± SEM, * $p < 0.05$)

3.3.2 Activity of neurons in the PCC track only the social status of the monkey in the sample image

We first examined whether neuronal activity of PCC neurons showed differential firing for sample images. Of the 59 neurons collected, 40.7% showed a face-selective response (n = 24). Of these, 16 neurons showed greater firing for subordinate sample faces as compared to dominant sample faces. 13 neurons showed this differential firing activity in the sample and target epochs, while the remaining 3 showed differential firing activity in the sample epoch only. 13.6% of neurons showed preferential firing for dominant faces (n = 8), with this differential firing being observed in both the sample and target image epochs. Two example neurons illustrating both population types have been shown in Figure 13. Of the task-responsive neurons, the majority (16 of 24 neurons) showed higher firing activity for subordinate faces as opposed to dominant faces (Figure 14B). This was also reflected at the level of averaged population firing rate. Population firing rate during the sample and target epochs was greater for subordinate sample images as opposed to dominant sample images (Figure 17A; normalized firing rate for subordinate sample: M = 1 Hz $\pm$ 0.056; normalized firing rate for dominant sample: M = 1.33 Hz $\pm$ 0.067; Student's t-test, $p < 0.01$).

When matching identity in this task, the critical social information was the individual identity of the sample monkey to be matched irrespective of its dominance

status. To see whether the identity of the monkey influenced the behavior of the subject and the firing of neurons in the PCC, we performed an ANOVA where the individual identity of the sample monkeys was included as an independent variable. No main effect of individual identity was observed, either at the level of behavior or at the level of firing of PCC neurons ($F = 0.05$, $p = 0.9$). Subjects could accurately identify all sample monkeys, irrespective of dominance status and individual identity. Additionally, neurons in the PCC fired in a binary fashion to face stimuli, showing significantly greater firing for subordinate faces.

3.3.3 Activity of neurons in the PCC does not track the trial outcome

We also assessed whether neuronal firing activity tracked trial outcome, that is, whether the monkey had made a positive identification or an error in identification. Of the 59 neurons tested, none of the neurons showed any difference in firing activity based on the trial outcome in any of the epochs analyzed (Normalized firing rate for correct trials: $M = 1$ Hz $\pm$ 0.032; normalized firing rate for error trials: $M = 0.98$ Hz $\pm$ 0.033, Student's t-test, $p = 0.81$). Although previous studies have shown that neurons in the PCC are highly sensitive to juice rewards and to omission of juice rewards (McCoy et al 2003, McCoy and Platt, 2005), these neurons do not seem to track trial outcome. While this is a surprising divergence from previous studies, one possible explanation is that I have sampled neurons more caudally within the PCC as compared to previous studies.

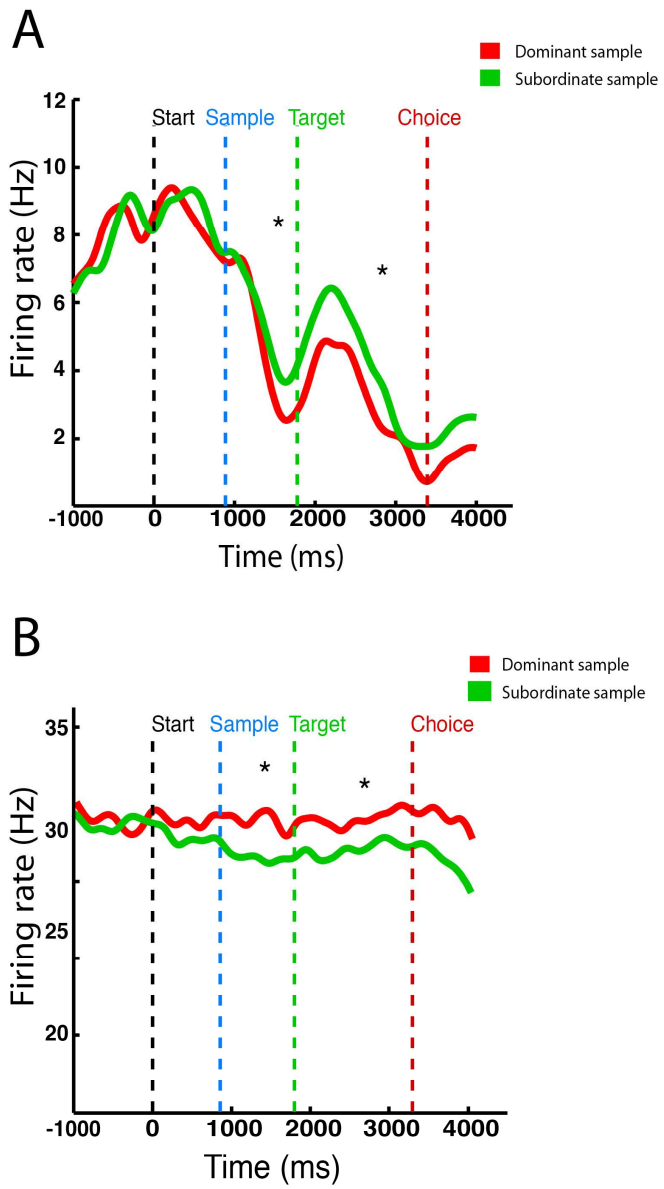

Figure 13: Example neurons showing differential firing activity for dominant and subordinate sample images. Individual neurons in the PCC show higher firing rates for either subordinate (A) or dominant (B) faces.

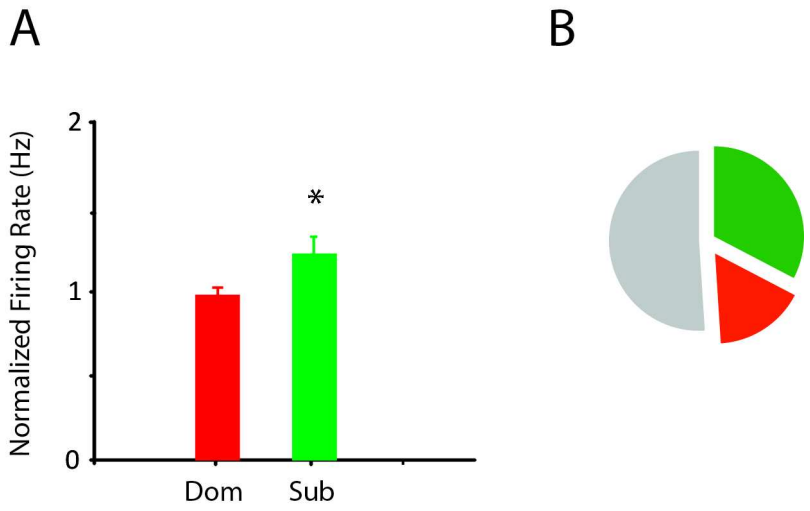

Figure 14: Population firing rate of neurons in the PCC to dominant or subordinate sample faces

(A) Average (normalized) firing rates of task-responsive neurons showing higher firing rates for subordinate faces as compared to dominant faces. (B) Individually, 66.7% of task responsive cells fired more for subordinate faces (green) while 33.3% fired more for dominant faces (red).

3.3.4 Neuronal activity in the PCC does not predict task engagement

As previously reported, neuronal activity in the PCC predicts task engagement, as measured by broken fixation trials (Hayden et al, 2009; Figure 8A). We asked whether the spontaneous neuronal activity preceding a trial predicted task engagement, by assessing the performance of subjects on error trials. There were two types of error trials: the first being errors due to incorrect identity matching, and the second being due to broken fixations (i.e. the subjects failed to complete the trial). Firing rates of neurons during the ITI epoch (500 ms preceding the start of each trial) were analyzed to observe whether they were predictive of subsequent task performance. Firing activity preceding

a trial did not predict whether the monkey would correctly match identity or not (Figure 15A; Normalized firing rate prior to correct trials: M = 1 Hz $\pm$ 0.19; normalized firing rate prior to error trials: M = 1.26 Hz $\pm$ 0.37; Student's t-test, p = 0.079). Similarly, pre-trial firing activity of neurons did not predict whether the subjects would successfully complete a trial (Figure 15B; Normalized firing rate prior to completed trials: M = 1.05 Hz $\pm$ 0.1; normalized firing rate prior to broken fixation trials: M = 1.13 Hz $\pm$ 0.25; Student's t-test, p = 0.3). Statistically, no relationship was found between firing rate prior to trial commencement and task engagement, though there was a non-significant trend to increase in spontaneous firing activity of neurons preceding trials where the subject failed to correctly identity the sample monkey.

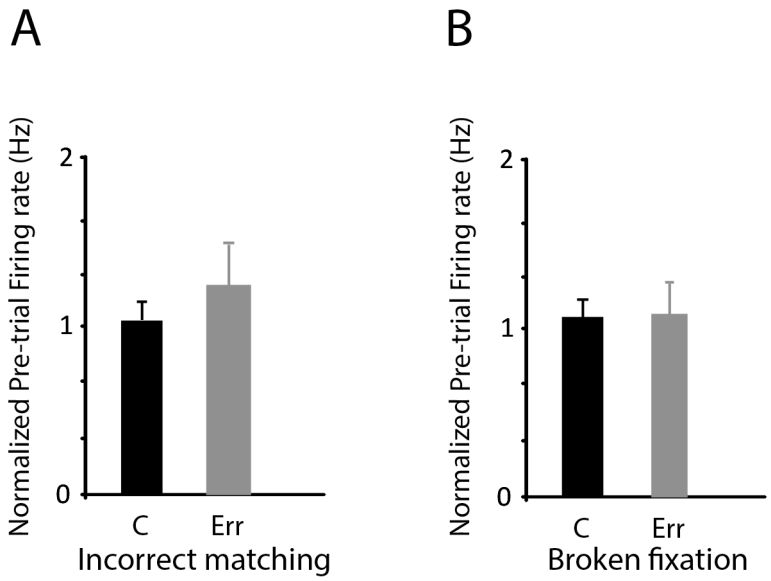

Figure 15: Neuronal activity preceding trial start did not predict task engagement

Normalized firing rates of neurons in a 500 ms ITI epoch preceding the start of trial did not predict subsequent task performance, in terms of accuracy (A) or successful completion of trials (B). (Data are represented as mean ± SEM)

3.4 Conclusion

Macaque monkeys attend to and can accurately match the identity of familiar monkeys irrespective of their social status. Their accuracy of matching and reaction times remain indistinguishable when matching the images of either dominant monkeys or subordinate ones. This has been previously reported for both macaques (Parr et al 2000, Parr et al 2010) and chimpanzees (Parr et al 2000, Parr 2003, Parr et al 2010). This current study is novel for employing several key features that distinguish it from

previous studies. Firstly, it uses more unique sample monkeys for identity matching. Next, a fairly large and frequently refreshed library of images per given identity was used for the purposes of matching, making it unlikely that subject monkeys learnt sets of images instead of learning the rule of matching individual identity. Finally, the laboratory set-up allowed for the collection of several thousands of trials over the course of the study, and, most importantly, allowed for sampling of neuronal activity from the PCC.

The responses of neurons in the PCC mimicked those seen in the prior distraction task (Chapter 2). Neuronal activity encoded the social status of the face monkeys viewed during the sample presentation period, with cells showing a higher firing rate for subordinate faces as opposed to dominant ones. The face stimulus in the current study was a task-relevant stimulus, while the dominance status of the monkey was a task-irrelevant stimulus. Subjects received identical amounts of juice for correctly identifying both dominant and subordinate faces. This equality was seen at the level of behavior, where subjects accurately matched and were equally attentive to faces of both dominant and subordinate individuals. Interestingly, at the level of neuronal firing, PCC neurons still tracked the dominance status of the face, despite the fact that dominance status did not inform behavior or trial outcome.

Activity in the PCC did not track task engagement, as indexed by errors made

and reaction times. This is in contrast to previously published studies (Hayden et al 2009) and to the results observed with the distraction task (see chapter 2). Spontaneous firing of PCC neurons predicts task engagement in the distraction task, and this was not observed in the match-to-identity task. However, it is important to note that a trend to increased firing rate predicting reduced task engagement was observed, though this trend was non-significant. It is possible that collecting more electrophysiological data will resolve this trend and so corroborate previous results.

To conclude, the neurons in the PCC tracked the social category of face stimuli in the match-to-identity task in a manner similar to that seen in the distraction task. Thus, neurons in the PCC track the value of social images, irrespective of whether they are task-relevant or influence behavior.

4. Reversible inactivation of the PCC does not affect social valuation

4.1 Introduction

PCC activity in response to non-social gustatory tasks has been well characterized. We know that the PCC encodes fluid reward (McCoy et al 2003), omission of reward (McCoy et al 2003), and the subjective value of a fluid reward (McCoy and Platt 2005). The firing of PCC neurons predicts the likelihood that a monkey will switch behavioral strategies in both a simple option-switching task (Hayden et al 2008) and a more complex one (Pearson et al 2009). Furthermore, firing rates in the PCC seems to maintain information about previous reward outcomes (McCoy and Platt 2005, Hayden et al 2008). Thus, the PCC appears to track and maintain strategically relevant information. Furthermore, microstimulation of the PCC increases the likelihood that subjects will switch their behavioural strategy (Hayden et al 2009). Collectively, the PCC appears to be participate in the circuit that tracks environmental demands and subsequently uses this information to modify behavior.

The PCC has also been implicated in attaching salience to social stimuli in addition to non-social gustatory rewards. We know that monkeys preferentially value the faces of dominant individuals, and show innate orienting towards the faces of dominant individuals. One possibility is that the PCC, in a manner similar to that seen for non-social rewards, tracks the subjective value of different social categorical

information and uses it to subsequently influence behavior. Indeed, our neurophysiological results support such a role for the PCC (see chapter 2). Neurons in the PCC track the categorical value of social stimuli (Figure 6, Figure 14), and do so despite social category being a task-irrelevant stimulus. Thus, if the PCC is responsible for attaching salience to social stimuli, and consequently motivating orienting behavior, silencing of the PCC should abolish the orienting behavior observed in the distraction task.

While our single unit recordings are extremely suggestive of the PCC playing a role in the valuation of social information, these results are correlational. We thus, injected GABA-agonist muscimol into the PCC, to study whether the innate preference that monkeys display for dominant faces is abolished following inactivation of the PCC.

4.2 Materials and Methods

4.2.1 Subjects

All procedures were in accordance with the guidelines established by Duke University's Institutional Animal Care and Use Committee and the Public Health Service's Guide for the Care and Use of Animals. The subjects were two male, adult rhesus macaques (*Macaca mulatta*) who were individually housed in a colony of 10 male macaques, all of whom had visual and auditory contact with each other. The subjects were fluid restricted outside of the experimental sessions.

4.2.2 Surgical procedures

Standard, sterile surgical techniques were performed. First, a head-restraining prosthesis (Crist Instruments) was implanted in subject monkeys. Subjects were allowed a 6-week recovery period, following which they were habituated to head-restraint and trained to perform occulomotor tasks for fluid reward. A second surgical procedure was undertaken to place a stainless steel recording chamber (Crist Instruments) over the PCC at the intersection of the interaural and midsagittal planes. Animals were provided antibiotics and analgesics for 10 days following all surgical procedures. The chamber was kept sterile with regular antibiotic rinses and sealed using replaceable, sterile caps (Crist Instruments).

4.2.3 Behavioural techniques

The horizontal and vertical eye-positions of head-restrained subjects were sampled at 1000 Hz by an infrared eye-monitoring camera system (SR Research, Osgoode, ON). Visual stimuli were presented on a computer monitor placed approximately 40 cm in front of the subject and centered on his eyes. Stimuli presentation was controlled using Matlab (Mathworks, Natick, MA) along with Psychtoolbox (Brainard 1997) and Eyelink Toolbox (Cornelissen et al 2002).

In order to determine whether the PCC plays a causative role in assigning value to social signals, we silenced the PCC using muscimol and observed the preference of subjects for images of different social categories. We made use of the distraction task

already covered in chapter 2 (Figure 2). The subjects made a choice between one of two fluid outcomes, and between one of two face stimuli. Upon successful completion of each trial, the juice reward was delivered to the subject by means of a tube. Juice delivery was measured in terms of 'solenoid open time' in ms.

A trial was initiated by fixating on a central fixation square. Following acquisition of fixation, two eccentric targets were presented. The colors of the targets indicated the juice reward associated with m, each juice value being represented by a unique color. Subject S was offered a choice between juice rewards of 125 ms versus 175 ms, while subject B was offered a choice between juice rewards of 145 ms versus 155 ms. The juice targets were on screen for 500 ms, following which two face stimuli were presented. Placement of the face stimuli was such that both the faces and juice targets were simultaneously visible. Subjects had a 1000 ms free-viewing period, during which they were free to view either of the two faces or juice targets. The face stimuli presented were either that of dominant monkeys or subordinate monkeys. Thus there were four choices available to the subjects: large juice reward/dominant face vs small juice reward/dominant face, large juice reward/dominant face vs small juice reward/subordinate face, large juice reward/subordinate face vs small juice reward/dominant face, and large juice reward/subordinate face vs small juice reward/subordinate face. At the end of the free-viewing period, juice reward was delivered to the subject based on the face and juice target he was looking at. On 10% of

the trials, no face stimuli were presented. Subjects were only presented with the juice targets and were required to make a choice between juice reward values without the distraction of face stimuli.

4.2.4 Face stimuli

A 4 megapixel camera (Nikon CoolPix 4600) was used to acquire all face stimuli. The images were of six monkeys that the two subjects were housed with. Using unidirectional submissive gestures, three were judged to be dominant to the two subject monkeys and three were judged to be subordinate. Only neutral facial images were used, with varying eye gaze and head direction. A few hundred images were used for each of the six monkeys. The heads were cropped and matched for size and luminance. The identities of the two monkeys to be used as face stimuli were chosen at random.

4.2.5 Reversible inactivation procedure

Reversible inactivation of the PCC was undertaken using muscimol, a GABA agonist (Sigma/Aldrich Chemicals). We injected 3 μg of muscimol (1 μg/μl dissolved in vehicle) unilaterally in the PCC. Injection was performed slowly to minimize irreversible damage to tissue. Injections were undertaken at 3 different sites each day (1 μg injected per depth, each site separated by a depth of 1000 μm). It has been observed that the effects of muscimol may last longer than 24 hours (Chowdhury and DeAngelis 2008, Hikosaka and Wirtz 1985), so all injections (whether muscimol or vehicle) were performed at least 48 hours apart. The behavioral session was initiated 30 minutes

following the injection of muscimol, and completed with 2.5 hours of initial injection of muscimol. Muscimol and vehicle injections were alternated and were always matched for side and sites. Subject S had 6 injections of muscimol and 6 injections of vehicle (injection schedule: MVMVMVMVMVMV). Subject B had 5 injections of muscimol and 5 injections of vehicle (injection schedule: VMVMVMVMVM).

4.3 Results

4.3.1 Reversible inactivation of the PCC does not alter differential valuation of face stimuli based on social status

Neurons in the PCC track the social status of monkey faces, with cells showing higher firing for subordinate faces as opposed to dominant ones. A similar signal is also seen in human imaging studies, where the PCC responds selectively to familiar faces (Phillips et al 1998, Shah et al 2000). It has been suggested that this signal in the PCC is important for attaching salience to social stimuli based on their social categories. If the PCC is indeed upstream of social valuation, silencing the PCC should abolish the preference behavior seen in monkeys based on social categories.

We first assessed whether muscimol-induced inactivation affected the juice valuation of subjects, by analyzing choice behavior on trials where only choice between juice targets was presented (without face stimuli). Subjects predominantly chose the larger juice reward, and this behavior was unaffected following muscimol inactivation (% chose larger juice for control: 80.7 $\pm$ 6.3; muscimol: 85.9% $\pm$ 7.2, Student's t-test p >

0.05).

We then assessed whether the innate preference monkeys show for dominant faces was affected. The time-course of muscimol inactivation proceeds from 5 – 10 minutes post injection and often extends for more then 24 hours (Chowdhury and DeAngelis 2008, Hikosaka and Wurtz 1985, Levy et al 2001). Our study was well within this time frame of muscimol action. Additionally, dividing the data into an early session and a late session did not affect results (Figure 16B, 2x2x2 ANOVA for early/late session, muscimol treatment, and face stimulus yielded only a significant main effect for the status of the face, see below).

Reversible inactivation of the PCC did not affect choice behavior, with animals showing a similar preference for dominant animals in the control condition and following inactivation (Figure 16). Both subjects showed a preference for large juice rewards, that was unaffected by muscimol. When the subjects were required to choose between a larger juice reward/subordinate face vs a smaller juice reward/dominant face, subjects were willing to sacrifice a small amount of juice reward in order to look at the dominant monkeys faces (This has been previously described in chapter 2, see Figure 4). Subjects chose the large juice reward 87% $\pm$ 6.3 of the time when it was associated with a dominant face, though this dropped to 68% $\pm$ 6 if the large juice was associated with a subordinate face. This pattern of choice behavior remained unaffected following muscimol injections in the PCC (2-way ANOVA, larger juice chosen with dominant face:

M = 85% ±10 and with subordinate face: M = 66% ± 13, p = 0.74).

4.3.2 Reversible inactivation of the PCC does not affect task performance

Activity in the PCC is known to predict task engagement as indexed by errors trials – trials a monkey is unable to successfully complete due to errors in fixation (Hayden et al 2009, Figure 8A). PCC inactivation did not affect the error rates observed in the distraction task (Student's t-test, error rate for control: M = 14.55 ± 1.67; error rate for muscimol: M = 17.03 ± 2, p = 0.6; Figure 17A).

We also assessed whether subjects attended to dominant and subordinate animals by looking at pupil sizes. Subjects attended equally to dominant (M = 1 ± 0.47) and subordinate (M = 1.05 ± 0.36) animals as indexed by pupil size, and silencing the PCC did not have any affect on this result (2-way ANOVA, following inactivation: dominant: M = 0.97 ± 0.63; subordinate = 1 ± 0.4; p > 0.5; Figure 17B). We also undertook 2x2x2 ANOVAs with social status of the face, associated juice reward, and experimental manipulation (muscimol or control) as factors to determine whether there was any effect on behavior; but no main or interaction effects were found on either the time taken to first saccade to a face stimulus or on pupil size when observing face stimuli.

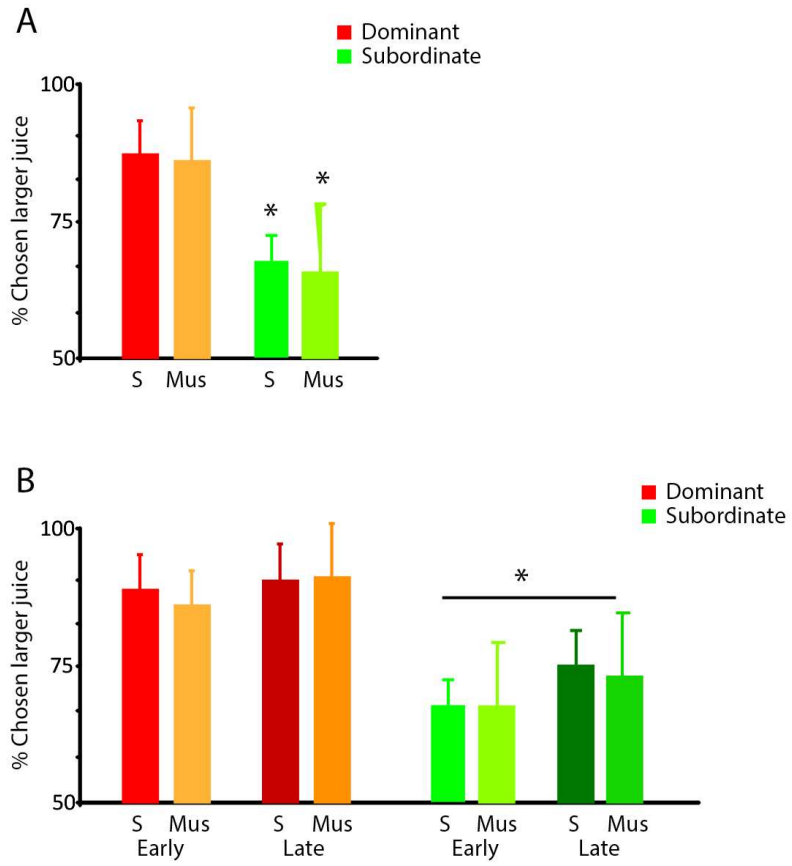

Figure 16: Reversible inactivation of the PCC did not alter preference behavior in the distraction task.

(A) Subjects preferred large juice rewards except in cases where a subordinate face was associated with larger juice amount and a dominant face associated with smaller juice amount, in which case subjects looked away from the large juice reward (dark green). This switch from a large juice reward/subordinate face and towards a small juice reward/dominant face was observed in even following muscimol inactivation. (B) The time during a session – early or late – did not impact either behavior or the effects of muscimol. (Data are represented as mean ± SEM).

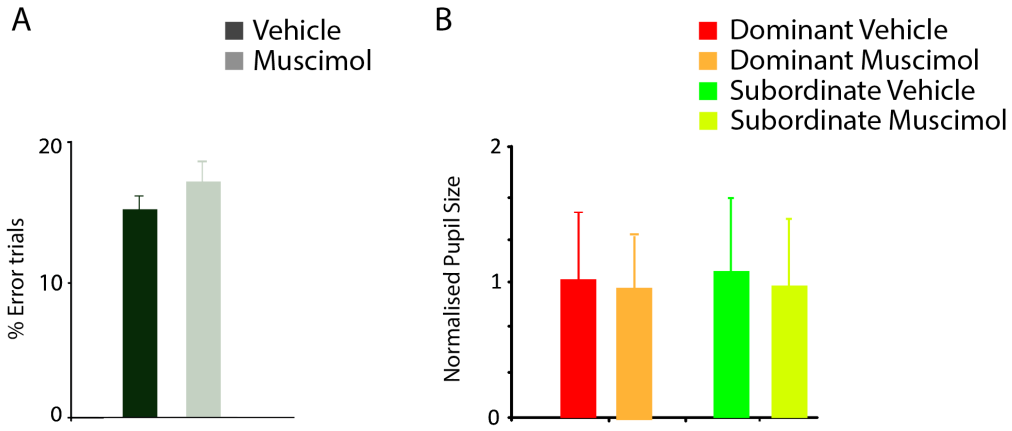

Figure 17: Reversible inactivation of the PCC did not affect task performance

(A) Muscimol inactivation did not result in task disengagement as indexed by unsuccessfully completed error trial (B) There was no effect of social status, muscimol treatment or interaction effect on pupil size. (Date are represented as mean ± SEM).

4.4 Conclusion

Our electrophysiological data (see chapter 2 and chapter 3) and imaging studies in humans show that the PCC is tracks social information (Leveroni et al 2000, Maddock et al 1999, Maddock et al 2001, Maddock et al 2003). It has been hypothesized that the PCC not only tracks the value of social categorical information, but uses this information to motivate behavior. One possibility is that the PCC attaches salience to social stimuli and so influences behavior, for instance the innate orienting behavior towards dominant faces observed in monkeys. However, reversible inactivation of the macaque PCC did not affect behavior in the distraction task. Monkeys sacrifice juice reward in order to

view the faces of dominant conspecifics, and inactivation of the PCC did not affect this orienting behavior (Figure 16), indicating that inactivation of the PCC did not affect valuation of social stimuli.

While the reversible inactivation of the PCC did not affect the orienting and choice behavior of monkeys, it remains difficult to prove the null hypothesis – the PCC does not play a role in social valuation and motivating behavior – as true. For a start, one major caveat of such muscimol inactivation studies must be taken into account. I employed unilateral injections of muscimol into the PCC and it is possible that the volume of the resulting inactivation is insufficient to impact behavior. Indeed, larger lesions encompassing the PCC in humans are known to affect several social cognitive processes, including the recall of autobiographical memory (Valenstein et al 1987), and valuation of face stimuli (Ellis and Young 1990). Furthermore, the PCC has been ascribed a causative role in tracking non-social fluid outcomes and using this information to update behavior (Hayden et al 2009, Pearson et al 2009). It would be surprising if the strong social categorical signal that we observe in the PCC is not reflective of a critical role for the PCC in social valuation and subsequent behavior modification.

Another point of note is the role of the PCC and the LIP. The PCC and the LIP share reciprocal connectivity (Kobayashi and Amaral 2003, Vogt et al 1992), though the LIP is external to the DMN. In fact, the LIP is considered to be part of the circuitry that

mediates attentional control (Corbetta et al 2002, Smith et al 2010). Activity in the PCC and LIP are anti-correlated (Fox et al 2005), increased activity in the PCC (and DMN) believed to promote broad monitoring of the environment and increased activity in the LIP promoting focused attention. The LIP is known to play a causal role in eye movement decisions; the LIP carries a "saliency map" of visual space and activity of neurons within the LIP biases eye movement towards the specific visual space represented by the neurons (Gold and Shadlen 2001). Indeed, microstimulation within the LIP biases eye movement decisions (Hanks et al 2009). Furthermore, LIP activity prior to a saccade encodes the expected value of the fluid reward of that saccade (Dorris and Glimcher 2004, Platt and Glimcher 1999). Thus, LIP activity appears to represent the value of orienting to a particular target. This appears to be generalizable to social stimuli, since LIP neurons also encode the value of social information (including dominance status) (Klein et al 2009). The increased activity in the LIP seen in response to dominant faces (Klein et al 2009) would drive orienting behavior towards dominant individuals. Conversely, the increased activity in the PCC in response to subordinate individuals (Figure 6) would drive a state change, perhaps allowing a more relaxed and flexible monitoring of the external environment. If this scheme holds true, then dominant individuals recruit the attentional circuits (including the LIP) to elicit focused attention, while subordinate individuals promote activity in the DMN (and PCC) and allow for a broad monitoring of the environment.

It remains impossible to conclusively rule out the PCC as underlying the valuation of social stimuli with this current inactivation study. A more extensive inactivation or permanent lesioning of the PCC might be warranted to better understand the causal role, if any, of the PCC. However, the robust activations seen in the PCC to the value of social and gustatory rewards, the causal role for the PCC in switching behavioral strategies, the centrality of the PCC in the DMN, and the pathologies associated with PCC dysregulation, collectively all argue for the PCC being a key mediator of social valuation and the subsequent social gating of attention.

5. General conclusions

5.1 Summary of data

Human imaging studies have implicated the PCC in encoding the value of non-social rewards (Hayden et al 2008, Kable and Glimcher 2007, McCoy and Platt 2005, Pearson et al 2009) as well as the value of social stimuli (Lane et al 1997, Phillips et al 1997). The role of the PCC in signaling the value of juice rewards has been further developed in animal models using single unit electrophysiological recordings (McCoy et al 2003, McCoy and Platt 2005, Hayden et al 2008). However, whether the individual PCC neurons also track the value of social stimuli in addition to non-social fluid rewards remains unknown. This thesis addresses this issue by investigating single unit activity of PCC neurons during valuation and categorization of conspecific social images.

I utilized two tasks in the course of this thesis. The first – the distraction task – was designed to probe the innate orienting of monkeys towards dominant faces as opposed to subordinate ones. This preference for dominant monkeys, demonstrated as the willingness to sacrifice fluid reward to view dominant faces, has been reported in previous studies from the lab (Deaner et al 2003, Klein et al 2005, Watson and Platt 2012). The second task – the match-to-identity task – was designed to study the ability of monkeys to accurately access the identity of individual monkeys. Thus, the two tasks probed two different aspects of face recognition: the value of faces (with the distraction task) and the overt identity of a face (the match-to-identity task). Based on the findings

from both tasks, we can draw several conclusions, which I shall summarize next.

5.1.1 Neuronal activity in the PCC tracks social information in preference to non-social fluid rewards

Previous studies have reported robust responses of PCC neurons to fluid rewards, including the delivery of reward (McCoy et al 2003), omission of rewards (McCoy and Platt 2005), the subjective value of rewards (McCoy and Platt 2005, Hayden et al 2008) and changes in reward choice strategies (Hayden et al 2009, Pearson et al 2010). Human imaging studies suggest that the PCC is responsive to non-social reward outcomes (Kable and Glimcher 2007) and to social stimuli (Lane et al 1997, Leveroni et al 2000, Phillips et al 1998, Shah et al 2000).

In our tasks, neurons in the PCC preferentially carry information about social stimuli. In the distraction task, 79.8% of task-relevant neurons responded to the social status and not to the fluid outcome. This prevalence of neurons encoding categorical social information is also seen in the match-to-identity task. All the task-responsive neurons track social category and none track the fluid outcome. Behaviorally, the juice reward still drives a subject's choice preferences far more than the social status of faces. However, far more neurons in the PCC track social status information as opposed to the juice value. Thus, there is a disconnect between the juice-driven behavior of monkeys and the tracking of social status by PCC neurons, and it appears that social information has preferential access to the PCC over fluid reward value.

5.1.2 Neuronal activity in the PCC tracks the value of social images, but not individual identity

In the model for face recognition proposed by Ellis and Young (Ellis and Young 1990), the PCC is involved in the affective recognition of faces. Human imaging studies show that the PCC is responsive to emotionally-salient social images (Lane et al 1997, Phillips et al 1997). Furthermore, single unit recordings demonstrate that PCC neurons track the subjective value of choices, albeit non-social ones (McCoy and Platt 2005). This thesis provides novel evidence that PCC neurons also signal the value of social stimuli.

Neuronal activity in the PCC is robustly correlated with the value of social images in, both, the distraction task and the match-to-identity task, and not individual identity. This is particularly interesting given the differences between the two tasks. The social stimulus is irrelevant to task-completion for the distraction task. However, subjects still display an inherent bias for orienting towards dominant faces. For the match-to-identity task, the social identity is crucial to task completion, and subjects can accurately match (and pay equal attention to) the faces of dominant and subordinate animals. The social status of a face has no appreciable effect on behavior in this task. However, cells in both tasks track the social status of faces. Thus neurons in the PCC track the social status of faces, irrespective of whether such social category information affects or enhances behavior.

5.1.3 Neuronal activity in the PCC and task engagement

The PCC is considered to be a central hub of the DMN and is believed to be critical for task engagement and focused attention (Buckner et al 2008). The DMN is characterized by task-related deactivations (Raichle et al 2001, Buckner et al 2008), and such deactivations are predictive of subsequent task performance (Eichele et al 2008). This has also been demonstrated using electrophysiological techniques in rhesus macaques, where suppressed neuronal firing is observed during periods of active task participation and higher spontaneous firing activity of PCC neurons is predictive of a subsequent lack of task engagement (Hayden et al 2009). Thus, increased activity within the PCC is inversely correlated with task engagement. This result has been corroborated in the distraction task, where higher spontaneous activity prior to the start of a trial precedes an unsuccessfully completed trial. However, results from the match-to-identity task do not support this observation. Firing of neurons during the pre-trial epoch does not predict subsequent task performance in terms of either successfully completed trials (trials in which monkeys did not look away from the fixation target prematurely and sucessfully indicated a choice) or incorrect trials (trials in which monkeys made an incorrect identity match).

In the next section of this chapter, I shall discuss the implications these results have on our understanding of PCC function.

5.2 The PCC, DMN, and social cognition

5.2.1 Posterior cingulate cortex and outcome evaluation

The PCC has been extensively studied and has been implicated in several neurological and psychiatric disorders including Alzheimer's disease, schizophrenia, and autism (Kennedy et al 2006, Minoshima et al 1997, Mitelman et al 2005, Northoff et al 2005, Valla et al 2001), but despite its seeming importance, there is no commonly recognized unified theory for the function of the PCC. However, several electrophysiological studies have indicated that the PCC plays a role in outcome evaluation: namely in monitoring reward outcomes and using that information to influence or guide future behavior.

PCC neurons respond to juice rewards (McCoy et al 2003) and one of the prevalent ideas for PCC function is that it tracks the subjective value of these rewards (Kable and GLimcher 2007, McCoy and Platt 2005). However, recent data discount this idea (Haeilbronner et al 2011). In a complex decision making task where monkeys make decisions varying on dimensions of reward value, risk, delay to reward, and social cues, the firing of PCC neurons did not track the subjective value of the rewards as indicated by the behavioral preferences of monkeys. The PCC neuronal activity in the distraction task complements these earlier studies. Around 10% of the neurons in the distraction task track the value of the juice reward, a prevalence similar to previous reports that around 30% of PCC neurons responded to the value of juice reward chosen (McCoy et al 2003). However, this tracking of juice value does not mirror behavioral preference.

Behaviorally, the preference of monkeys varies along both the face stimulus and juice reward axes, such that they prefer dominant faces over subordinate ones and larger juice rewards over smaller ones. Thus, if neurons track the subjective preferences of monkeys, they would integrate information about the presented face stimulus and the juice reward. However, this is not borne out by the data, with cells encoding either the social status of faces or the juice reward value. Thus, in keeping with data from the Heilbronner study, cells in the PCC do not appear to encode the subjective value of outcomes.

In addition to tracking reward outcomes, it has also been suggested that firing in the PCC signals subsequent changes in behavioral strategies. Neurons in the PCC show higher activity prior to a switch in choice strategy in a simple choice task (Hayden et al 2008). Furthermore, this can also be generalized to a more complex choice task (Pearson et al 2009), in which the firing of PCC neurons signals in a graded fashion upcoming changes in behavioral strategy. Thus, it has been suggested that neurons in the PCC track strategically relevant information that is then used to implement a change in behavioral choice strategy. We can look at whether the firing of neurons in the PCC affects the choice behavior in the distraction task, where monkeys can choose between the faces of either dominant or subordinate monkeys or between two juice rewards. Firing of the neurons prior to the start of a trial does not predict the subsequent choice behavior of monkeys. Thus, data from the distraction task does not support a role for the

PCC in signaling future changes in choice behavior. However, there is an interesting difference in task design to be considered at this juncture. The non-social choice task (McCoy et al 2005, Hayden et al 2008) requires monkeys to choose between a range of risky options and a standard safe option, with each level of risk being presented in a block of around 10-15 trials. Thus, the reward outcome on each trial contains information about the reward choices available to the monkey on subsequent trials. In contrast, while I only used a single juice reward option in the distraction task, the faces that are presented with the juice targets are randomly assigned. Essentially, each trial is independent of previous trials and the outcome of a trial does not inform the choice available to the monkey on subsequent trials. Thus, it would be reasonable to assume that the PCC tracks and signals changes in behavioral strategy only under task conditions where current reward outcomes inform future available options. A causal role for the PCC in change in behavioral strategy has also been demonstrated by perturbing PCC function (Hayden et al 2008). Microstimulation of the PCC prior to the start of a trial results in monkeys switching their choice strategy on the following trial. This further bolsters the idea that the PCC governs and is required for changes in behavioral strategy, though several caveats of the microstimulation protocol need to be considered. Firstly, the change in behavioral strategy following microstimulation is small (a 3.14% change in switching behavior). Additionally, the PCC is reciprocally connected with many brain regions implicated in reward monitoring and decision-

making, including the ACC. Microstimulation (Amemori and Graybiel 2012) and lesions (Kennerley et al 2006) of the ACC both affect reward-guided choice behavior. Thus, one possibility is that microstimulation within the PCC results in an increase in activation in the ACC via stimulation of the ACC afferents that innervate the PCC, and it is this unintentional stimulation of the ACC that affects choice behavior.

Taken collectively, the PCC does not track the subjective value of outcomes and may not necessarily signal future changes in behavioral strategy. One possibility is that the PCC signals decision salience, this being the degree to which available outcomes deviate from each other. This would explain the PCC activity seen in non-social reward tasks where the firing rates of neurons track the degree to which a chosen outcome deviates from the second, non-chosen option, for example the risky option over the standard safe option or the delayed reward over one available immediately (McCoy and Platt 2005, Hayden et al 2008, Heilbronner et al 2011). In keeping with this idea, cells in the PCC also track the salience of social information. Individual PCC neurons show differential firing for monkey faces based solely on the social status of the face. We know that monkeys preferentially orient towards the faces of dominant animals (Chance 1967, Deaner et al 2005, Shepherd et al 2008) and value the faces of dominant animals more than subordinate ones (Chapter 2, Deaner et al 2005, Klein et al 2008). The neuronal firing rate reflects this disparity in preference for faces depending on social status, with PCC neurons showing higher firing activity for subordinate faces as compared to

dominant ones. Thus, it appears that the PCC signals the salience of reward outcomes, be they social or non-social.

5.2.2 Posterior cingulate cortex and task performance

The PCC is believed to be a central hub of the DMN and activity in the DMN has been linked to task engagement (Buckner et al 2008), and the extent of deactivation of the DMN has been shown to predict subsequent performance on tasks (Eichele et al 2008, Hayden et al 2009, Raichle et al 2001). Spontaneous neuronal activity within the PCC is predictive of a subsequent decrease in task performance as measured by error trials and slower reaction times (Hayden et al 2009). Data from the distraction task is consistent with these previous reports, where an increase in spontaneous pre-trial firing rates of PCC neurons signals a subsequent decrease in task performance. However, this pattern of activity is not seen in the match-to-identity task. Pre-trial firing activity of neurons does not predict subsequent task performance, either at the level of a successfully completed trial or a correct identity match trial.

One explanation for this difference in spontaneous PCC activity is the cognitive load associated with the different tasks. The match-to-identity is a cognitively challenging task; in contrast, both the distraction task and the non-social risk choice task only require simple choice behavior. It is possible that cognitively challenging tasks show greater recruitment of the frontoparietal attentional network, and this increased cognitive control results in a tighter regulation of the PCC, with a resulting decrease in

variability of spontaneous activity within the PCC during non-task conditions. This is supported by imaging data from humans, wherein activity within the DMN changes with cognitive load and the functional connectivity between the attentional networks and the DMN increases with increasing cognitive loads (Leech and Sharp 2013, Newton et al 2010).

5.2.3 Default mode network and social cognition

The results from the distraction task and the match-to-identity task strongly suggest a role for the PCC in social cognition and in, specifically, signaling the attentional value or salience of other individuals. Given the centrality of the PCC in the DNM, this also has interesting implications for the DMN.

The DMN was first described and characterized as a group of brain regions with high hemodynamic and metabolic activity when the subject was not actively engaged in a task (Buckner et al 2008, Ingvar 1974, 1979, 1985). Further studies demonstrated that in addition to high activity in the rest state, these brain regions underwent deactivations prior to active task participation (Buckner et al 2008, Eichele et al 2008, Gusnard and Raichle 2001, Raichle et al 2001, Raichle and Mintun 2006). However, in addition to the consistent deactivations seen prior to task participation, brain regions linked to DMN, including the PCC, are also actively recruited in a certain subset of tasks: those involving social cognition. They show increased activity in response to tasks relying on social

cognitive processes, including recall of autobiographical memories (Andreason et al 1995, Maguire et al 2001), self-referential thinking (Buuren et al 2010), theory of mind (Fletcher et al 1995, Riling et al 2004, Saxe and Powell 2006), and social and moral decision-making (Greene et al 2001). The substantial overlap in brain regions recruited in social cognition and the DMN has led to the suggestion that the DMN serves a primarily social function.

Several authors have suggested that primate intelligence is biased towards social information processing over non-social information (Cosmides and Tooby 1994, Jolly 1966, Mesoudi et al 2006). Thus primates have a predisposition for social cognition, particularly when freed from the constraints of a specific task, and this would be reflected in the activity of the DMN. In keeping with this hypothesis, the PCC – a key component of the DMN – displays preferential coding of social information. Despite erstwhile reactivity to the value of fluid rewards (McCoy et al 2003, McCoy and Platt 2005, Hayden et al 2008), when presented with social stimuli, the majority of task-responsive cells in the PCC track the value of social information.

It would not be entirely surprising if social cognition recruits the DMN. The DMN is characterized by the presence of several rich "nodes", cortical regions that have a high degree of reciprocal connectivity with several other brain regions (Hagmann et al 2008). The PCC itself is connected with brain structures that are involved in autobiographical memory recall, learning, attention, and emotionality (Vogt et al 1979,

Vogt et al 1992, Yukie and Shibata 2009). The DMN would thus be ideally suited to track complex and constantly changing stimuli, as would be found in the social milieu of primates. A key aspect of successfully living in a social group is keeping track of the social hierarchy within the group (De Waal 1982, Cheney and Seyfarth 2008). The DMN, with access to systems including those of autobiographical memory and individual identity, would be particularly beneficial in tracking social hierarchies. My results showing that the PCC signals social hierarchical information provide an initial insight into this aspect of social cognition.

One possible role of this social hierarchical information within the PCC would be in the social gating of attention. Social status is known to gate social attention in humans (Dalmaso et al 2012) and in non-human primates (Shepherd et al 2008). This has been demonstrated in a laboratory setting, where macaques are willing to sacrifice juice reward to view the faces of dominant individuals (Deaner et al 2005, Klein et al 2009, Watson and Platt 2012, results presented in this thesis) and reflexively follow the gaze of high-status monkeys (Shepherd et al 2008). Thus, macaques are attentive to dominant animals, and this seems to be an innate, untrained behavior. Data from field research corroborates this. It appears that a key component of maintaining hierarchical rank orders within a social group involves the constant attention that subordinates pay to the more dominant individuals (Chance 1967). Within our current understanding of the DMN, dominant individuals would drive a decrease in DMN activity, since such

decreases signify focused attention (Buckner et al 2008, Eichele et al 2008). My data corroborates this idea, with decreased PCC neuronal activity signaling a dominant face and increased activity signaling a subordinate face.

In the context of a more naturalistic environment, it is possible that the lack of dominant individuals allows for a broad monitoring of the environment. Chance (1967) noted that macaques, in the presence of dominant members of their social group, constantly shifted their gaze towards the dominant individuals. It appears that social status gates attention such that dominant individuals require focused attention, while a lack of dominant individuals would allow for a broad monitoring of the environment. Thus, decreased activity in the PCC would allow for focused attention on dominant individuals, while increased activity to subordinate individuals results in a more general monitoring of the environment. Data from non-social tasks does support this role for DMN function. In tasks that necessitate choosing between two global strategies, DMN activity is associated with exploratory choices while suppressed DMN activity is associated with exploitative choices (Daw et al 2006, Pearson et al 2009). Furthermore, there is greater activation within the DMN in tasks that require attending to parafoveal or diffuse targets as opposed to foveal ones (Shulman et al 1997). Thus, the social status of individuals gates the attention behavior of macaques, with dominant individuals promoting deactivation of the DMN and focused attention, and subordinate individuals promoting increased DMN activity and a broad monitoring of the environment.

The PCC, within the context of social hierarchies, appears to process information related to individuals that do not necessitate high levels attention. A similar distinction between high-priority and low-priority states is seen in the learning of reward value associations. Inactivation of the PCC hampers associative learning in macaques, but only when the rewards involved are of low value (Heilbronner 2012). Thus a second possibility is that the DMN might be preferentially involved in processing only low-priority information, namely subordinate faces.

5.2.4 Social value versus individual identity

Monkeys display an innate preference for images of dominant animals compared to subordinate animals (Deaner et al 2003, Klein et al 2005, Watson and Platt 2012). This is an inherent and untrained bias towards high-status individuals. Neuronal activity in the PCC tracks the social value of a face (i.e. its dominance status), but not its overt identity. The PCC neurons classify faces in a binary fashion, with higher firing being observed for subordinate faces as opposed to dominant ones. Interestingly, this binary firing pattern is seen in both the distraction task and the match-to-identity task, despite subjects displaying incredibly different behaviors in the two tasks. Monkeys seem to inherently orient to dominant faces as opposed to subordinate ones in the distraction task, while in contrast, they attend equally to dominant and subordinate faces in the match-to-identity task. Despite these two distinct behavioral strategies, the activity of most neurons in both tasks reflects the social value of the face stimulus and not its

identity.

The most widely accepted models for face perception (Bruce and Young 1986, Ellis and Young 1990) treat the extrastriate cortices involved in face perception as distinct modular domains, each being responsible for a particular aspect of face

perception. The fusiform face area (FFA) and the lateral fusiform gyrus are believed to extract the invariant information present in faces, namely the identity of a face (Haxby et al 2000, Hoffman and Haxby 2000, Sergent et al 1992). In contrast, the STS and the PCC are believed to extract affective information associated with faces. The STS tracks variant aspects of face perception, including eye-gaze direction and expression (Engell and Haxby 2007, Hasselmo et al 1989, Hoffman and Haxby 2000, Puce et al 1998). The PCC, in contrast, is believed to extract the affective information associated with faces, including familiar faces (Leveroni et al 2000, Phillips et al 1998, Shah et al 2000) and emotionally salient faces (Phillips et al 1998). The current electrophysiological results support the idea of modularity in face perception systems; the neuronal activity in the PCC signals categorical social values and not individual identity.

5.3 Future directions

An important conclusion that can be drawn from these studies is that the DMN serves a predominantly social function. Neurons in the PCC predominantly respond to the social salience of stimuli, as opposed to gustatory reward outcomes. However, the

experiments designed here did not account for and distinguish between all potential salience and attention signals. For instance, subjects were only offered a single juice reward choice on every trial. Thus, it is possible that while the majority of PCC neurons tracked only the social status of faces, a more complex choice paradigm involving several juice reward choices would result in a greater number of PCC neurons encoding the value of juice outcomes. Thus, one avenue for further study would be systematically varying the juice reward outcomes presented with the face stimuli to assess the impact on neuronal activity in the PCC.

Additionally, my studies have not demonstrated causation. Inactivation of the PCC does not affect orienting behavior in the distraction task. It is possible that the PCC merely serves as a signal of the state of an organism, and does not serve a causal role in mediating the orienting behavior towards dominant individuals. However, it is difficult to rule out a causal role for the PCC based solely on the inactivation study undertaken here. A change in inactivation protocol, by extending the area of PCC affected by the inactivation, might well yield significant behavioral effects. This would be an advantageous avenue for further study. If the PCC is indeed involved in mediating socially gated attention, perturbations in the PCC should affect behavioral preference in the distraction task, while the identity matching in the match-to-identity task should remain unaffected. It is also possible that the distraction task used here is not sensitive enough to detect changes in behavior following inactivation of the PCC. Perhaps a better

assessment of disrupted PCC behavior would be observing the interactions between animals, using controlled pair-wise confrontations, following inactivation of the PCC.

5.4 Final remarks

There is reason to believe that the default mode of the primate brain is one of social cognition. The salience of social stimuli (namely, the dominance status of individuals) gates the attention of monkeys, with high-status individuals recruiting attention and low-status individuals allowing for a disengagement from focused attention. One way this social gating of attention might occur is via recruitment of the PCC and the DMN. Social stimulation affects activity in the DMN in a category-specific manner, the DMN then changing the state of an organism to either one of focused attention or a general monitoring of the external environment based on the social status of observed individuals. This would require social status to affect DMN activity in very specific ways: with dominant faces suppressing DMN activity and resulting in a subsequent focusing of attention, and subordinate faces allowing for higher DMN activity that is associated with more broad attention. Support for the DMN mediating the social gating of attention comes from my data looking at the activity of neurons in the PCC in response to social stimuli. PCC neurons track the salience of social stimuli, with the population of PCC neurons showing higher firing for subordinate faces as compared to dominant ones, and this pattern of activity is consistent with the hypothesized role for the DMN in mediating socially-gated attentional states.

References

Altmann S (1967) in *Social Communication Among Primates*, ed Altmann SA, University of Chicago Press

Amemori A and Graybiel AM (2012) Localized microstimulation of primate pregenual cingulate cortex induces negative decision-making *Nature Neurosci* 15:776-785.

Amiez C, Joseph JP, Procyk E (2005) Anterior cingulate error-related activity is modulated by predicted reward. *Eur J Neurosci* 21:3447-52.

Andreasen NC, O'Leary DS, Cizadlo T, Arndt S, Rezai K, et al. (1995) Remembering the past: two facets of episodic memory explored with positron emission tomography *Am J Psychiatry* 152:1576–85.

Beer JS, John, OP, Scabini D, Knight RT (2006) Orbitofrontal cortex and social behavior: integrating self-monitoring and emotion- cognition interactions *J Cogn Neurosci* 18, 871–879.

Berson RJ (1983) Capgras' syndrome *Am J Psychiatry* 140:969-78.

Bonte FJ, Harris TS, Roney CA, Hynan LS (2004) Differential diagnosis between Alzheimer's and frontotemporal disease by the posterior cingulate sign. *J Nucl Med* 45:771-4.

Breen N, Caine D, Coltheart M (2000) Models of face recognition and delusional misidentification: a critical review *Cogn Neuropsychol* 17: 55–71.

Brookmeyer R, Gray S, Kawas C (1998) Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset *Am J Public Health* 88(9):1337-42.

Bruce V, Young A (1986) Understanding face recognition *Br J Psychol* 77:305–27.

Buckner RL, Andrews-Hanna JR, Schacter DL (2008) The brain's default network: anatomy, function, and relevance to disease *Ann NY Acad Sci* 1124:1-38.

Buckner RL, Carroll DC (2007) Self-projection and the brain. *Trends in cognitive sciences* 11:49-57.

Buckner RL, Vincent JL (2007) Unrest at rest: default activity and spontaneous network correlations. *NeuroImage* 37:1091-6; discussion 7-9.

Burgess PW, Veitch E, de Lacy Costello A, Shallice T (2000) The cognitive and neuroanatomical correlates of multitasking. *Neuropsychologia* 38:848-63.

Carmichael ST, Price JL (1995) Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys *J Comp Neurol* 363(4):615-641.

Chance MRA (1967) Attention structure as the basis of primate rank orders Man 2:503-518.

Cicerone KD, Tanenbaum LN (1997) Disturbance of social cognition after traumatic orbitofrontal brain injury. Arch. *Clin. Neuropsychol*. 12, 173–188.

Citron M (2004) Strategies for disease modification in Alzheimer's disease *Nature Rev Neurosci* 5:677-685.

Corbetta M, & Shulman GL (2002). Control of goal-directed and stimulus-driven attention in the brain *Nat Rev Neu* 3:201–15.

Corkin S (1980) in The psychosurgery debate: scientific, legal and ethical perspectives. Ed Valenstein ES, San Fransisco WH, pp 164-204

Critchley H, Daly E, Phillips M, Brammer M, Bullmore E, Williams S, Van Amelsvoort T, Robertson D, David A, Murphy D (2000) Explicit and implicit neural mechanisms for processing of social information from facial expressions: a functional magnetic resonance imaging study *Human Brain Mapping* 9:93-105

Dalmaso M, Pavan G, Castelli L, Galfano G (2012) Social status gates social attention in humans *Biol Letters* 8:450-452.

Daselaar SM, Prince SE, Cabeza R (2004) When less means more: deactivations during encoding that predict subsequent memory *NeuroImage* 23:921-7.

Daw ND, O'Doherty JP, Dayan P, Seymour B, Dolan RJ (2006) Cortical substrates for exploratory decisions in humans. *Nature* 441:876–879.

Deaner RO, Khera AV, Platt ML (2005) Monkeys pay per view: adaptive valuation of social images by rhesus macaques *Current biology : CB* 15:543-8.

Deaner RO, Platt ML (2003) Reflexive social attention in monkeys and humans. *Current biology : CB* 13:1609-13.

Dorris MC and Glimcher PW (2004) Activity in posterior parietal cortex is correlated

with the relative subjective desirability of action *Neuron* 44(2): 365-78.

Dougherty DD, Baer L, Cosgrove GR, Cassem EH, Price BH et al (2002) Prospective long term follow-up of 44 patients who received cingulotomy for treatment-refractory obsessive compulsive disorder *Am J Psychiatry* 159(2):269-75.

Eichele T, Debener S, Calhoun VD, Specht K, Engel AK, et al (2008) Prediction of human errors by maladaptive changes in event-related brain networks. *Proceedings of the National Academy of Sciences of the United States of America* 105:6173-8.

Ellis HD, Lewis MB (2001) Capgras delusion: a window on face recognition *Trends Cog Sci* 5:149-56.

Ellis HD, Young AW (1990) Accounting for delusional misidentifications *Br J Psychiatry* 157:339-48.

Engell AD, Haxby JV (2007) Facial expression and gaze-direction in human superior temporal sulcus *Neuropsychologia* 45:3234-3241.

Eslinger, PJ, Damasio, AR (1985) Severe disturbance of higher cognition after bilateral frontal lobe ablation: patient EVR. *Neurology* 35, 1731–1741.

Fletcher PC, Happe´, F. Frith U, Baker SC, Dolan RJ, et al. (1995) Other minds in the brain: A functional imag- ing study of "theory of mind" in story comprehension *Cognition* 57:109–28.

Fink GR, Markowitsch HJ, Reinkemeier M, Bruckbauer T, Kessler J, Heiss WD (1996) Cerebral representation of one's own past: neural networks involved in autobiographical memory. *J neurosci* 16:4275-82.

Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks *Proc. Natl. Acad. Sci. U.S.A.* 102:9673–9678

Garrity AG, Pearlson GD, McKiernan K, Lloyd D, Kiehl KA, Calhoun VD (2007). Aberrant "default mode" functional connectivity in schizophrenia *Am J Psychiatry* 164:450–7.

Ghatan PH, Hsieh JC, Wirsen-Meurling A, Wredling R, Eriksson L, et al. (1995) Brain activation induced by the perceptual maze test: a PET study of cognitive performance. *Neuroimage*, *2*:112–24.

Gilbert SJ, Dumontheil I, Simons JS, Frith CD, Burgess PW (2007) Comment on "Wandering minds: the default network and stimulus-independent thought". *Science* 317:43.

Gilbert SJ, Simons JS, Frith CD, Burgess PW (2006) Performance-related activity in medial rostral prefrontal cortex (area 10) during low-demand tasks. *J Exp Psychol Hum Percept Perform* 32:45-58.

Gold JI, Shadlen MN (2001) Neural computations that underlie decisions about sensory stimuli *Trends Cogn Sci* 5(1):10-16.

Greene JD, Sommerville RB, Nystrom LE, Darley JM, Cohen JD (2001) An fMRI investigation of emotional engagement in moral judgment. *Science* 293:2105–8.

Grön G, Wunderlich AP, Spitzer M, Tomczak R, Riepe MW (2000) Brain activation during human navigation: gender-different neural networks as substrate of performance. *Nat Neurosci* 3:404 – 408.

Gusnard DA, Akbudak E, Shulman GL, Raichle ME (2001) Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function *Proceedings of the National Academy of Sciences of the United States of America* 98:4259-64.

Gusnard DA, Raichle ME (2001) Searching for a baseline: functional imaging and the resting human brain *Nat Rev Neurosci 2:*685–94.

Hahn B, Ross TJ, Stein EA (2007) Cingulate activation increases dynamically with response speed under stimulus unpredictability *Cereb Cortex* 17:1664–71.

Hafkemeijer A, van der Grond J, *et al.* (2012). Imaging the default mode network in aging and dementia. Biochim. Biophys. Acta 1822 (3): 431-41.

Hanks TD, Ditterich J, et al. (2006) Microstimulation of macaque area LIP affects decision-making in a motion discrimination task *Nat Neurosci* 9(5): 682-9.

Harley CA, Bielajew CH (1992) A comparison of glycogen phosphorylase a and cytochrome oxidase histochemical staining in rat brain *J Comp Neurol* 322(3):377-89.

Hasselmo ME, Rolls ET, Baylis GC (1989) The role of expression and identity in the face-selective responses of neurons in the temporal visual cortex of the monkey *Behav*

Brain Res 32:203–218

Haxby JV, Petit L, Ungerleider LG, Courtney SM (2000) Distinguishing thefunctional roles of multiple regions in distributed neural systems for visual working memory *Neuroimage* 11:145–56.

Hayden BY, Heilbronner SR, Nair AC, Platt ML (2008) Cognitive influences on risk-seeking by rhesus macaques. *Judgm Decis Mak* 3:389-95.

Hayden BY, Nair AC, McCoy AN, Platt ML (2008) Posterior cingulate cortex mediates outcome-contingent allocation of behavior. *Neuron* 60:19-25.

Hayden BY, Smith DV, Platt ML (2009) Electrophysiological correlates of default-mode processing in macaque posterior cingulate cortex *PNAS*

Heilbronner S, Hayden B, Plat ML (2011) Decision salience signals in the posterior cingulate cortex *Frontiers Neurosci* 5:1-9.

Heilbronner S (2012) Neurobiology of learning and valuation

Hirono N, Mori E, Ishii K, Ikejiri Y, Imamura T (1998) Hypofunction in the posterior cingulate gyrus correlates with disorientation for time and place in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 64:552-4.

Hoffman EA, Haxby JV (2000) Distinct representations of eye gaze and identity in the distributed human neural system for face perception *Nat Neurosci* 3:80-4.

Hornak J, Rolls ET, Wade D (1996) Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. Neuropsychologia 34, 247–261.

Hornak J, Bramham J, Rolls ET, Morris RG, O'Doherty J, Bullock, PR, Polkey CE (2003) Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. Brain 126, 1691–1712.

Huang C, Wahlund LO, Svensson L, Winblad B, Julin P (2002) Cingulate cortex hypoperfusion predicts Alzheimer's disease in mild cognitive impairment *BMC Neurol* 2:9.

Hulshoff Pol HE, Schnack HG, Mandi RC, van Haren NE, Koning H, Collins DL, Evans AC, Kahn PS (2001) Focal gray matter density changes in schizophrenia *Arch Gen Psychiatry* 58(12)1118-25.

Ingvar DH (1974) Patterns of brain activity revealed by mea- surements of regional cerebral blood flow. *Alfred Benzon*

Ingvar DH (1979) "Hyperfrontal" distribution of the cerebral grey matter flow in resting wakefulness: on the functional anatomy of the conscious state. *Acta Neurol Scand* 60:12– 25.

Ingvar DH (1985) "Memory of the future": an essay on the temporal organization of conscious awareness. *Hum Neu- robiol* 4:127–36.

Kable JW, Glimcher PW (2007) The neural correlates of subjective value during intertemporal choice. *Nature neuroscience* 10:1625-33.

Katayama K, Takahashi N, Ogawara K, Hattori T. 1999. Pure topographical disorientation due to right posterior cingulate lesion *Cortex* 35:279-82.

Kelley WM, Macrae CN, Wyland CL, Caglar S, Inati S, Heatherton TF (2002) Finding the self? An event-related fMRI study *J Cogn Neurosci*14:785– 94.

Kennedy DP, Redcay E, & Courchesne E (2006) Failing to deactivate: resting functional abnormalities in autism *Proc Natl Acad Sci* 103:8275–80.

Kennerley SW, Walton ME, Behrens TEJ, Buckley MJ, Rushworth MFS (2006) Optimal decision making and the anterior cingulate cortex *Nature Neurosci* 9:940-947.

Klein JT, Deaner RO, Platt ML (2008) Neural correlates of social target value in macaque parietal cortex *Curr Biol* 18:419–424.

Kobayashi Y Amaral DG (2003) Macaque monkey retrosplenial cortex: II. Cortical afferents. *J. Comp. Neurol*. 466:48–79.

Lane RD, Reiman EM, Bradley MM, Lanp PJ, Ahern GL, Davidson RJ, Schawrtz GE (1997) Neuroanatomical correlates of pleasant and unpleasant emotion *Neuropsychologia* 35:1437-44.

Leech R and Sharp DJ (2013) The role of the posterior cingulate cortex in cognition and disease *Brain*.

Leveroni CL, Seidenberg M, Mayer AR, Mead LA, Binder JR, Rao SM (2000) Neural systems underlying the recognition of familiar and newly learned faces *J Neurosci* 20:878–86.

Maddock RJ (1999) The retrosplenial cortex and emotion: new insights from

functional neuroimaging of the human brain *Trends Neurosci* 22:310-16.

Maddock RJ, Buonocore MH (1997) Activation of left posterior cingulate gyrus by the auditory presentation of threat-related words: an fMRI study. *Psychiatry research* 75:1-14.

Maddock RJ, Garrett AS, Buonocore MH (2001) Remembering familiar people: the posterior cingulate cortex and autobiographical memory retrieval. *Neuroscience* 104:667-76.

Maddock RJ, Garrett AS, Buonocore MH (2003) Posterior cingulate cortex activation by emotional words: fMRI evidence from a valence decision task. *Hum Brain Mapp* 18:30-41.

Maguire EA (2001) Neuroimaging studies of autobiographical event memory *Philos Trans R Soc Lond B Biol Sci* 356:1441–51.

Mars RB, Neubert FX, Noonan MAP, Sallet S, Toni I, Rushworth MFS (2012) On the relationship between the "default mode network" and the "social brain" *Fron in Human Neurosci* 6:1-9.

Mason MF, Norton MI, Van Horn JD, Wegner DM, Grafton ST, Macrae CN (2007) Wandering minds: the default network and stimulus-independent thought. *Science* 315:393-5.

McCoy AN, Crowley JC, Haghighian G, Dean HL, Platt ML (2003) Saccade reward signals in posterior cingulate cortex. *Neuron* 40:1031-40.

McCoy AN, Platt ML (2005) Risk-sensitive neurons in macaque posterior cingulate cortex. *Nature neuroscience* 8:1220-7.

Mesoudi A, Whiten A, Dunbar R (2006) A bias for social information in human cultural transmission *Brit J Pcych* 97(3):405-423.

Mesulam M (2000) Principles of behavioral and cognitive neurology

Minoshima S, Giordani B, Berent S, Frey K, Foster NL, Kuhl DE (1997) Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease *Ann Neurol* 42:85-94.

Mitelman SA, Shihabuddin L, Brickman AM, Hazlett EA, Buchsbaum MS (2005) Volume of the cingulate and outcome in schizophrenia *Schizophr Res* 72:91-108.

Mitchell JP, Macrae CN, Banaji MR (2006) Dissociable medial prefrontal contributions to judgments of similar and dissimilar others *Neuron* 50:655–63.

Murphy K, Birn RM, Handwerker DA, Jones TB, Bandettini PA (2009) The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? *Neuroimage* 44:893–905.

Murray EA, Davidson M, Gaffan D, Olton DS, Suomi S (1989) Effects of fornix transection and cingulate cortical ablation on spatial memory in rhesus monkeys. *Exp Brain Res* 74:173-86.

Narumoto J, Okada T, Sadato N, Fukui K, Yonekura Y (2001) Attention to emotion modulates fMRI activity in human right superior temporal sulcus *Cog Brain Research* 12:225-31

Newell KA, Deng C, Huang XF (2006) Increased cannabinoid receptor density in the posterior cingulate cortex in schizophrenia *Exp Brain Res* 172:556-60.

Newell KA, Zavitsanou K, Huang XF (2005) Ionotropic glutamate receptor binding in the posterior cingulate cortex in schizophrenia patients *Neuroreport* 16:1363-7.

Newell KA, Zavitsanou K, Jew SK, Huang XF (2007) Alterations of muscarinic and GABA receptor binding in the posterior cingulate cortex in schizophrenia *Prog Neuropsychopharmacol Biol Psychiatry* 31:225-33.

Newton AT, Morgan VL, Rogers BP, Gore JC (2010) Modulation of steady state functional connectivity in the default mode and working memory networks by cognitive load *Human Brain Mapp* 32(10):1649-1659.

Northoff G, Richter A, Bermpohl F, Grimm S, Martin E, et al (2005) NMDA hypofunction in the posterior cingulate as a model for schizophrenia: an exploratory ketamine administration study in fMRI *Schizophr Res* 72(2-3):235-48.

Olson CR, Musil SY (1992) Posterior cingulate cortex: sensory and oculomtor properties of single neurons in the behaving cat. *Cereb Cortex* 2:485-502.

Olson CR, Musil SY, Goldberg ME (1996) Single neurons in posterior cingulate cortex of behaving macaque: eye movement signals. *Journal of neurophysiology* 76:3285-300.

Padoa-Schioppa C, Assad JA (2006) Neurons in the orbitofrontal cortex encode economic value *Nature* 441:223–226.

Papez JW (1937) A proposed mechanism of emotion *Neuropsychiatry Clin Neurosci* 7(1):103-12.

Parr LA (2003) Discrimination of faces and their emotional content by chimpanzees (Pan troglodytes) *Ann N Y Acad Sci* 1000:56-78

Parr LA, de Waal FBM (1999) Visual kin recognition in chimpanzees *Nature* 399:147-648

Pearson JM, Hayden BY, Raghavachari S, Platt ML (2009) Neurons in posterior cingulate cortex signal exploratory decisions in a dynamic multioption choice task *Current biology : CB* 19:1532-7.

Perrett DI, Smith PAJ, Potter DD, Mistlin AJ, Head AS, Milner AD, Jeeves MA (1985) Visual cells in the temporal cortex sensitive to face view and gaze direction *Proc Royal Soc Lond B* 223:293-317.

Phillips ML, Bullmore ET, Howard R, Woodruff PWR, Wright IC, et al (1998) Investigation of facial recognition memory and happy and sad facial expression perception: an fMRI study *Psychiatry Res: Neuroimg Sec* 83:127-138.

Phillips ML, Young AW, Senior C, Brammer M, Andrew C, Calder AJ, Bullmore ET, et al. (1997) A specific neural substrate for perceiving facial expressions of disgust *Nature* 389(6650):495-498.

Platt ML and Glimcher PW (1997) Responses of intraparietal neurons to saccadic targets and visual distractors *J Neurophysiol* 78(3): 1574-89

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001) A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America* 98:676-82.

Raichle ME, Mintun MA (2006) Brain work and brain imaging *Annu Rev Neurosci* 29:449–476.

Reiman EM, Caselli RJ, Yun LS, Chen K, Bandy D, Minoshima S, Thibodeau SN, Osborne D (1996) Preclinical evidence of Alzheimer's disease in persons homozygous for the E4 allele for apolipoprotein *E New Engl J Med* 334:752-758.

Rilling JK, Sanfey AG, Aronson KA, Nystrom LE, & Cohen JD (2004) The neural correlates of theory of mind within interpersonal interactions *Neuroimage*, *22*:1694–703.

Rudebeck PH, Buckley MJ, Walton ME, Rushworth MFS (2006) A role for the macaque anterior cingulate gurus in social valuation *Science* 313:1310-12.

Rushworth MF, Behrens TE (2008) Choice, uncertainty and value in prefrontal and cingulate cortex. *Nature neuroscience* 11:389-97.

Saxe R, Carey S, Kanwisher N (2004) Understanding other minds: linking developmental psychology and functional neuroimaging *Annu Rev Psychol* 55:87–124.

Saxe R, Powell LJ (2006) It's the thought that counts: specific brain regions for one component of theory of mind *Psychol Sci* 17:692–9.

Schilbach L, Eickhoff SB, Rotarska- Jagiela A, Fink GR, Vogeley K (2008) Minds at rest? Social cog- nition as the default mode of cog- nizing and its putative relationship to the default system of the brain.*Conscious Cogn* 17:457–467.

Schultz W, Dayan P, Montague PR (1997) A neural substrate of prediction and reward. *Science* 275:1593-9.

Schoenbaum G, Roesch M (2005) Orbitofrontal cortex, associative learning, and expectancies. *Neuron* 47:633-6.

Sergent J, Ohta S, MacDonald B (1992) Functional neuroanatomy of face and object processing: a positron emission tomography study *Brain* 115:15–36.

Shah NJ, Marshall JC, Zafiris O, Schwab A, Zilles K, Markowitsch HJ, Fink GR (2000) The neural correlates of person familiarity: A functional magnetic resonance imaging study with clinical implications *Brain* 124(4):804-815.

Shimizu E, Hashimoto K, Ochi S, et al (2007) Posterior cingulate gyrus metabolic changes in chronic schizophrenia with generalized cognitive deficits *J Psychiatr Res* 41(1-2):49–56.

Shepherd SV, Deaner RO, Platt ML (2008) Social status gates social attention in monkeys *Curr Bio* 16(4):119-120

Shulman GL, Fiez JA, Corbetta M, Buckner RL, Miezin FM, et al (1997) Common blood flow changes across visual tasks: II.: decreases in cerebral cortex *J Cogn Neu* 9:648–63.

Smith DV, Davis B, Niu K, Healy EW, Bonilha L, et al (2010) Spatial attention evokes

similar activation patterns for visual and auditory stimuli *J Cogn Neurosci* 22:347–361.

Smith, Kosslyn (2007) Cognitive Psychology: Mind and Brain 21(194-199).

Sorg C, Reidl V, Muhlau M, Calhoun VD, Eichele T, et al (2007) Selective changes of resting-state networks in individuals at risk for Alzheimer's disease *Proc Natl Acad Sci* 104:18760–5.

Sowell ER, Levitt J, Thompson PM, Holmes CJ, Blanton RE, et al (2000) Brain abnormalities in early-onset schizophrenia spectrum disorder observed with statistical parametric mapping of structural magnetic resonance images *Am J Psychiatry* 157(9):1475-84.

Spreng RN, Grady CL (2010) Patterns of brain activity supporting autobiographical memory, prospection, and theory of mind, and their relationship to the default mode network. *Journal of cognitive neuroscience* 22:1112-23.

Squire LR, Stark CEL, Clark RE (2004) The medial temporal lobe *Annu Rev Neurosci* 27:279-306.

Sutherland RJ, Whishaw IQ, Kolb B (1988) Contributions of cingulate cortex to two forms of spatial learning and memory *J Neurosci* 8(6):1863-72.

Svoboda E, McKinnon MC, Levine B (2006) The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia* 44:2189- 208

Tremblay L, Schultz W (1999) Relative reward preference in primate orbitofrontal cortex *Nature* 398:704–708.

Valenstein E, Bowers D, Verfaellie M, Heilman KM, Day A, Watson RT (1987) Retrosplenial amnesia *Brain : a journal of neurology* 110(6):1631-46.

Valla J, Berndt JD, Gonzalez-Lima F (2001) Energy hypometabolism in posterior cingulate cortex of Alzheimer's patients: superficial laminar cytochrome oxidase associated with disease duration *The Journal of neuroscience : the official journal of the Society for Neuroscience* 21:4923-30.

Van Buuren M, Gladwin TE, Zandbelt BB, Kahn RS, Vink M (2010) Reduced functional coupling in the default-mode network during self-referential processing *Human Brain Mapp* 31(8):1117-27.

Vogt BA, Finch DM, Olson CR (1992) Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. *Cereb Cortex* 2:435-43.

Vogt BA, Rosene DL, Pandya DN (1979) Thalamic and cortical afferents differentiate anterior from posterior cingulate cortex in the monkey. *Science* 204:205-7.

Wallis JD, Miller EK (2003) Neuronal activity in primate dorsolateral and orbital prefrontal cortex during performance of a reward preference task *Eur J Neurosci* 18:2069–2081.

Watson KK, Platt ML (2012) Social Signals in Primate Orbitofrontal Cortex. *Current Biology* 22:2268-2273.

Watson KK, Ghodasra JH, Platt ML (2009) Serotonin transporter genotype modulates social reward and punishment in rhesus macaques *PLoS ONE* 4:e4156.

Weissman DH, Roberts KC, Visscher KM, Woldorff MG (2006) The neural bases of momentary lapses in attention. *Nature neuroscience* 9:971-8.

Wicker B, Michel F, Henaff MA, Decety J (1998) Brain regions involved in the perception of gaze: a PET study *Neuroimage* 8:221-7.

Willis ML, Palermo R, Burke D, McGrillen K, Miller L (2010) Orbitofrontal cortex lesions result in abnormal social judgements to emotional faces. Neuropsychologia 48, 2182–2187.

Yoshiura T, Mihara F, Ogomori K, Tanaka A, Kaneko K, Masuda K (2002) Diffusion tensor in posterior cingulate gyrus: correlation with cognitive decline in Alzheimer's disease *Neuroreport* 13:2299-302.

Yukie M, Shibata M (2009) Temporocingulate interactions in the monkey. In *Cingulate Neurobiology and Disease*, ed. BA Vogt, pp. 146-58®. London: Oxford University Press.

Zhou Y, Dougherty JH, Jr., Hubner KF, Bai B, Cannon RL, Hutson RK (2008) Abnormal connectivity in the posterior cingulate and hippocampus in early Alzheimer's disease and mild cognitive impairment. *Alzheimers Dement* 4:265-70.

Biography

Amrita Nair was born in Mumbai, India in 1982. She received her BS in Biology in 2003 from Mumbai University in 2003, and her MS in Biology (focused on neurobiology) from the Tata Institute of Fundamental Research in 2003. While at Duke she was supported by a J.B. Duke Fellowship Award, and a research grant to Professor Platt from the National Institutes of Mental Health. She has held memberships in the Society for Neuroscience, the J.B. Duke Program, and the Steering Committee for Graduate Training in Neurobiology. She continues her training as a postdoctoral scholar under the guidance of Professor Steve Chang at Yale University.

Publications

Benekareddy M, Vadodaria KC, Nair AR, Vaidya VA (2011) Postnatal serotonin type II receptor blockade prevents the emergence of anxiety behavior, dysregulated stress-induced immediate early gene responses, and specific transcriptional changes that arise following early life stress. *Biol Psychiatry* 70(11):1024-1032.

Hayden BY, Heilbronner SR, Nair AC, Platt ML (2008) Cognitive influences on risk-seeking by rhesus macaques. *Judgm Decis Mak* 3:389-95.

Hayden BY, Nair AC, McCoy AN, Platt ML (2008) Posterior cingulate cortex mediates outcome-contingent allocation of behavior. *Neuron* 60:19-25.

Nair A, Vadodaria KC, Banerjee SB, Benekareddy M, Dias BG, et al (2007) Stressor-specific regulation of distinct brain derive nurotrophic factor (BDNF) transcripts and cyclic AMP response element binding protein (CREB) expression in the postnatal and adult rat hippocampus *Neuropsychopharmacol* 32:1504-1509.

Nair A, Vaidya VA (2006) Cyclic AMP response element binding protein and brain-derived neurotrophic factor: Molecules that mediate our mood? *J Biosci* 31(3):423-

434.

Santhanoori M, Dias B, Nair AR, Banerjee SB, Tole S, Vaidya VA (2004) Differential regulation of multiple brain derived neurotrophic factor transcripts by antidepressants in the adult rat brain *Neuropharm* 45:553-563.